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"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL I

Graham Smith, Editor 1987–1997

This issue of the *British Journal of Anaesthesia* (*BJA*) is the first for more than 10 yr that has not been edited, or co-edited, by Graham Smith. The board expect members of the editorial team to serve the journal unstintingly and the cult of personality is strongly deprecated. However, it would be remiss not to mark Graham Smith's sustained and distinguished contribution to the success of the journal.

In July 1997, the journal published an editorial in which Graham Smith outlined the major changes in the *BJA* during the tenure of his editorship. From this impressive catalogue I wish to emphasize just two aspects. First, the excellent TEAL CD-rom (the Electronic Anaesthetic Library) which was initiated by the *BJA* and *Anesthesia and Analgesia* before we were joined by *Anesthesiology* and the *Canadian Journal of Anaesthesia*. The speed with which this project was brought to a successful conclusion was a result, in no small part, to the fruitful co-operation between the four editors. It was an object lesson to see apparently rival journals working together to provide an important anaesthetic resource. Second, the *BJA* has increased inexorably in size in the past 10 yr and yet the editorial office coped seemingly effortlessly with the increased workload. This was the result mainly of the efficiency of the editorial team that Graham Smith appointed in Leicester and the board acknowledge their important contribution to the journal.

What of the man? His loyalty and dedication to the welfare of the *BJA* were unwavering. You attacked the journal at your peril, particularly if your facts were incorrect. He listened carefully to a reasoned argument, thought about the problem, discussed it widely and sometimes changed editorial policy. His impartiality in making difficult decisions about publication of a manuscript was unquestionable, as many members of the board can testify. At major anaesthetic meetings he would lecture, chair a session and then retire to a quiet place to edit manuscripts for the next publication deadline. All this editorial work was undertaken while continuing to write textbooks, examine, serve on the Council of the Royal College of Anaesthetists and build Leicester into one of the foremost academic departments in the country.

Graham Smith is clearly a workaholic, but this is allied to an original sense of humour. The situation of the *BJA* was occasionally desperate, but never serious, and his ability to maintain a sense of proportion during the difficult days helped him enjoy the good days even more. A passion for opera and mountains provided an escape from editorial pressures and

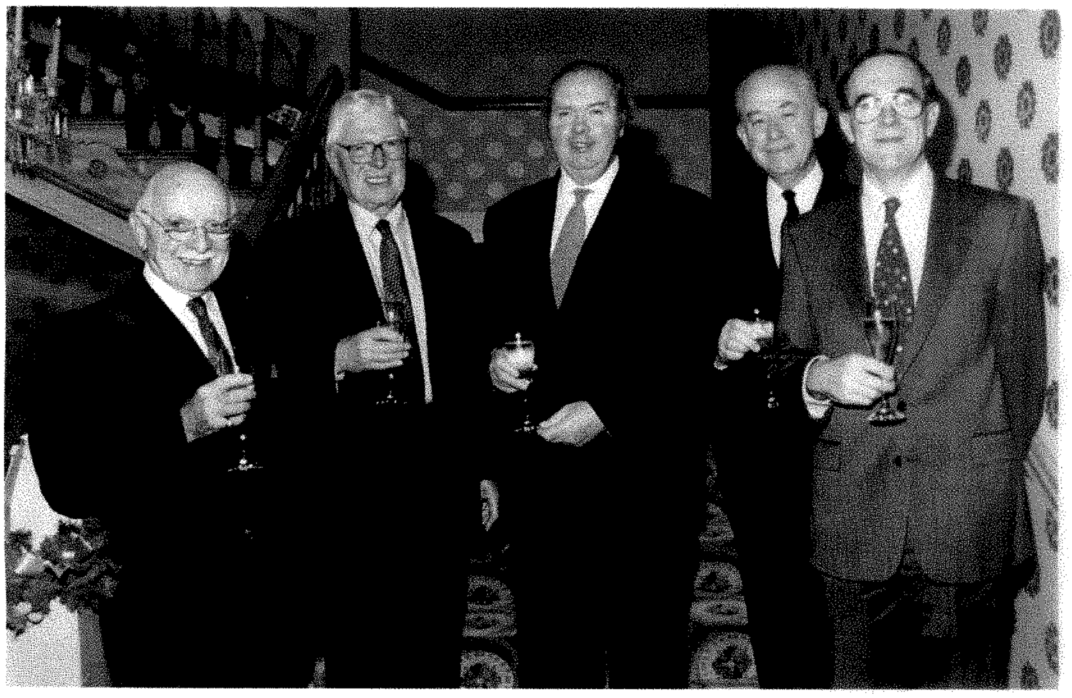

Figure 1 A half-century of editors. From left to right: T. Cecil Gray, joint editor 1947–1958, editor 1958–1963; J. Edmund Riding, editor 1963–1973; William Fitch, editor 1983–1987; Alastair A. Spence, editor 1973–1983; Graham Smith, editor 1987–1997.

it was pleasing to note in the recent editorial that he viewed the editorship as a particularly happy time in his professional life. Graham Smith has gained a unique insight into the behaviour of many senior anaesthetists around the world, having observed them as authors and assessors. I can only hope that he uses this information discreetly. I for one will have to maintain courteous relations for many years to come.

What happens to previous editors of the BJA? The photograph (fig. 1) shows that they continue to enjoy good health and good company. It was a pleasure to see five editors at a small celebration in 1995 and this group provided 50 years of editorship of the *BJA*, 1947–1997. Graham Smith was the eighth editor of the *BJA*; he will be a hard act to follow.

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IMPORTANT NOTICE TO AUTHORS

Change in drug labelling

The *British Journal of Anaesthesia* will be implementing a change in drug labelling from British approved names to international non-proprietary names, in accordance with the new recommended nomenclature, as described in: Navarro FA. *British Medical Journal* 1996;**313**:688.
This will take effect from January 1, 1998.

British Journal of Anaesthesia 1998; **80**: 415–416

EDITORIAL II

Pain after amputation: is prevention better than cure?

"Truly, it is a thing wondrous, strange, and prodigious which will scarce be credited, unless by such have seen with their own eyes and heard with their own ears, the patients who many months after cutting away the leg, grievously complained that they yet felt exceeding great pain in that leg so cut off"

Ambrose Paré (1510–1590) French military surgeon.[1]

The phenomenon of phantom pain is well recognized and, although usually thought of in the context of limb amputation, has also been described after removal of other parts of the body such as the breast.[2] The exact incidence is unclear, with values ranging from almost zero to nearly 100% being quoted in the literature.[3] Terminology is in part responsible for this disparity, as several types of sensation may be experienced after amputation. Distinction between phantom sensations, phantom pain and stump pain is important not only to allow the magnitude of the problem to be estimated accurately, but also because the management of these distinct clinical entities may be quite different.

Non-painful sensations are frequently experienced in the area of the amputated part. Such "phantom sensations" occur early and are so common that their presence may be considered normal. Intensity varies from, in their most vivid form, the perceived presence of an exact replica of the limb which can be moved at will, to a more vague awareness of the amputated part, or specific sensations such as itching of the toes. "Telescoping", whereby the image of the limb shrinks towards the stump, occurs over months or years. Although not painful, these phantom sensations are alarming to an unprepared patient who expects to feel nothing where the limb had previously existed. After operation there may be reluctance on the part of the individual to broach the subject with medical or nursing staff, and some patients may even question their own sanity. Preoperative preparation and reassurance that continues into the postoperative period is clearly an important aspect of perioperative care.

Pain localized to the amputation stump may be a result of several factors. Immediately after surgery, postoperative pain is expected; it may be exacerbated by infection or tissue necrosis. Later, poorly fashioned stumps and ill-fitting prostheses may cause problems. The formation of neuromata at the site of severed nerves causes localized tenderness and "electric shock" pain. Muscle spasms are troublesome in some patients and others may develop a complex regional pain syndrome (reflex sympathetic dystrophy). Surgical expertise, skilled limb fitting and careful rehabilitation may be preventative. Otherwise, treatment is aimed at the cause.

True "phantom pain" is a neuropathic pain perceived in the territory of the amputated limb. In common with other pain states, there is a spectrum of intensity. It is recognized that gradual remission occurs over time[4]; this may be of some comfort to those afflicted. However, this is not always the case and for a significant group of amputees (approximately 10%)[4,5] the pain persists in a severe form resulting in great suffering, disability and misery. Those anaesthetists working in the field of pain management will be familiar with such patients who usually present with a combination of phantom and stump pain. Many treatments have been tried. Sherman, Sherman and Gall[6] carried out a survey of treatments offered for phantom limb pain in the USA and identified 50 in current use. This in itself indicates that treatment is difficult, with no single therapy offering universal benefit. A process of trial and error usually identifies drugs or injection treatments that are beneficial in alleviating some of the pain. Tricyclic antidepressants and antiepileptic drugs are often used as first-line therapy for this and other types of neuropathic pain. A multidisciplinary approach is needed when the individual has developed the complex psychological morbidity and social consequences of long-term disability from chronic pain. Input from non-medical personnel such as the psychologist, physiotherapist and occupational therapist may enable the amputee to cope better and rehabilitate to an improved level of function.

Anaesthetists may encounter problems with amputees when undertaking regional anaesthesia. It has been recognized for 50 yr that both phantom sensations and phantom pain may occur during apparent complete neural block.[7] More recently, further case reports have confirmed this as a potential problem. It is associated primarily with subarachnoid and extradural anaesthesia,[7–15] although it has also been reported in the upper limb during brachial plexus block.[16] The phantom pain usually develops shortly after the onset of regional block, although in some cases it is delayed until neural block regresses. Preoperative experience of phantom limb pain appears to be a poor predictor of risk; the problem occurs in both patients with minimal and with troublesome pre-existing phantom pain. A variety of treatments have been tried to alleviate the induced pain, including transcutaneous nerve stimulation, systemic or spinal opioids, benzodiazepines, lidocaine, calcitonin and subanaesthetic doses of thiopental, with varying degrees of success. The extreme distress experienced by some patients, in one case necessitating conversion to general anaesthesia, led some authors to argue that lower limb amputation should be regarded as a contraindication to spinal anaesthesia.[7–9] This view has been contested by Tessler and Kleinman[17] who studied 23 spinal anaesthetics in lower limb amputees and found only a single case of significant induced phantom pain during the regional block. Whether or not amputation is considered a contraindication to spinal anaesthesia, it is clearly an area that needs careful consideration when choosing the most appropriate anaesthetic technique and contingency plan for an individual patient.

The most tantalizing aspect of phantom limb pain is whether it can be prevented. Nearly a decade has passed since this was first suggested by Bach, Noreng and Tjéllden.[18] His group was interested in the recognition that some phantom limb pain was of similar character and site to that experienced before amputation. In a prospective clinical study, one group was maintained in a pain-free state for 24 h before amputation using continuous lumbar extradural block. A control group was given oral analgesia to provide preoperative pain relief. At follow-up, none of the patients in the extradural group had phantom limb pain at 6 months or 1 yr. This contrasted with the control group in which 38% had phantom limb pain at 6 months ($P<0.05$) and 27% at 1 yr ($P<0.20$). Further evidence to support this notion of a pre-emptive effect comes from a more recent study of similar design.[19] Patients who were given extradural infusion of bupivacaine, clonidine and diamorphine for 1–2 days before operation and at least 3 days after operation, had less phantom limb pain than a control group who received on demand opioid analgesia. At both 6 months and 1 yr follow-up, one patient (8%) in the extradural group had phantom limb pain compared with eight (73%) in the control group ($P<0.002$).

Other preliminary work has been produced that supports a prophylactic effect of pre-emptive extradural block.[20] Given the morbidity that a sizeable proportion of amputees suffer, this would appear to be an attractive therapeutic strategy. The published work to date involves small numbers and does not provide the definitive answer to the question "does preoperative lumbar extradural block prevent phantom limb pain?" This question needs to be answered as the use of extradural infusions is not without risk. There are also resource implications, but the potential for cost savings if a benefit proved to be real. How long should the patient be rendered pain free in the perioperative period and what is the best combination of drugs? This is an area that needs further investigation. Prevention is better than cure, especially as cure is not an option for some of these patients.

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EDITORIAL III

Onset times and intubating conditions

The study by Fuchs-Buder, Sparr and Ziegenfuß[1] in this month's issue of the journal concludes that etomidate, as part of an induction regimen containing alfentanil and rocuronium, attenuates the reaction to intubation to a greater extent than thiopental. This would seem to concur with earlier findings by Gill and Scott[2] who related the difference in onset time of neuromuscular block observed with vecuronium to better maintenance of haemodynamic variables associated with etomidate compared with thiopental. This hypothesis is supported by previous work by Goat and colleagues[3] in dogs who noted that the time to maximum block after injection of gallamine decreased if blood flow was increased. Under normal conditions, muscle blood flow increases when cardiac output increases. Thus a relationship between speed of onset and cardiac output might be expected. This may also explain, at least in part, why infants and children demonstrate a faster onset of action of neuromuscular blocking drugs than adults.[4] The advantage of using etomidate in this situation must be balanced against possible inhibition of corticosteriod synthesis in the adrenal cortex of adults.[5]

How important is the onset time of neuromuscular blocking agents? This is one of the most extensively studied and reported pharmacodynamic variables in anaesthetic pharmacology, partly because of the relative ease in objectively assessing onset time with neuromuscular monitoring devices and partly because of the large number of possible dosing permutations in which these drugs may be administered. While some of this information is clinically important much is, at best, academic.

There is really only one reason why we need this information and that is to carry out equipotent comparisons between different neuromuscular blocking agents in the hope that we might relate these data to the relative speed and ease by which we can pass a tracheal tube during rapid sequence induction or during a potentially difficult intubation. Studies reporting onset times under conditions other than those similar to rapid sequence induction would seem to be of limited value. What clinical relevance is the onset time of a neuromuscular blocking agent during inhalation anaesthesia? Furthermore, much of the information pertaining to the adductor pollicis muscle does not represent the effect of neuromuscular blocking agents on other muscle groups, in particular the diaphragm, masseters, orbicularis oculae and the larynx.[6–9]

Grading of intubating conditions seems to measure what we need to know but most scientists would be uncomfortable about its objectivity and sensitivity. The wide between-patient variability in response to neuromuscular blocking agents is well recognized and the mean value for grade of intubation or onset time can therefore only be seen as an approximate indication of the response that might be achieved. It is also recognized that administering a dose of these water soluble agents on a weight-related dose basis may not be the most accurate method for calculating the appropriate dose and indeed contributes to the variability in response. An obese patient will be overdosed relative to a thin one. In the context of rapid sequence induction, studies should always provide the range of onset times and intubating conditions in order to anticipate the worst possible scenario and to allow the anaesthetist to decide on the suitability of the drug.

Priming, timing, dose and design have a varying contribution to play in accelerating onset and facilitating intubating conditions. Jones concluded that the potential problems associated with priming probably outweigh its advantages.[10] Those determined to use mivacurium may use the timing approach, which is reported to achieve intubation in 60 s with a combination of priming and top-up doses.[11] Others, however, have found divided dosing with this drug to be less effective.[12] This seems unnecessarily complicated when a similar effect in terms of onset time can be achieved with one dose of rocuronium. Administering the neuromuscular blocking agent before the induction agent[13] is another technique for reducing the time to intubation but the potential hazards of this approach need no elaboration.

High-dose regimens with all non-depolarizing neuromuscular blocking agents have been reported but none achieves rapid onset times as consistently as succinylcholine.[14 15] Rocuronium does, however, come close and if this drug is to be used for rapid sequence induction, a dose of at least 0.9 mg kg^{-1} should be administered,[16] although inevitably there will be prolongation in duration of effect. The addition of alfentanil to the induction technique would also seem to improve intubating conditions.[17] Extrapolation of these studies would suggest that the fastest onset times and best intubating conditions are obtained with a combination of etomidate, alfentanil and high-dose rocuronium, although this has yet to be shown. However, if this approach is to be used the anaesthetist should have the necessary plan, skills and equipment prepared for the failed intubation or worse still, the impossible airway. The advantages of rocuronium are less obvious in the situation where rapid sequence is not indicated. The 30 s saved on intubating time can hardly justify the use of the drug pharmacoeconomically unless priced at the same level and packaged in equipotent volumes as the cheaper, intermediate duration drugs.

With regard to drug design, the low potency aminosteroids seem to have the most rapid onset times and approach most closely the onset time of succinylcholine.[18] Unfortunately, as the potency of these drugs decreases, the margin of safety for cardiovascular side effects, in particular vagolysis, tends to decrease. It has also been suggested that as the time to achieve a biophase concentration to occupy 80% of receptors in the case of a non-depolarizing agent must be longer than that needed to achieve 20% occupancy for effect in the case of succinylcholine, depolarizing agents will always be intrinsically faster in onset.[19] Nevertheless, new non-depolarizing neuromuscular blocking agents continue to be produced in the hope of achieving a safe alternative to succinylcholine.[20]

These factors all have their role to play in accelerating onset and facilitating intubating conditions, but ultimately it is up to the anaesthetist to carry out a risk–benefit analysis of each situation before deciding on the ideal intubation cocktail. While every resident should be able to recite 10 side effects or contraindications of succinylcholine, the experienced anaesthetist should have a list of diminishing indications. The major side effects of succinylcholine are often only far too obvious, but even experienced anaesthetists may not be completely aware of the incidence of myalgia at 24–48 h. This has become much more relevant with the increasing amount of day surgery.

What are the indications for succinylcholine? It is still an important drug for the lone trainee and there are few, if any, hospitals in the UK that can claim 100% supervision by consultants. In the event that tracheal intubation cannot be achieved and ventilation by face mask is difficult, the rapid offset of succinylcholine allows spontaneous ventilation to resume. As experience is gained, the indications become less hard and fast and other options become attractive, in particular those that render the patient more safe or remove the potential morbidity and mortality associated with succinylcholine. While it is entirely appropriate for colleges of anaesthesia and textbooks to recommend firm guidelines, it is becoming increasingly inappropriate to be prescriptive to the consultant or staff anaesthetist. There are too many contentious areas. Operating outside "The Bolam Test" however, could be unwise.[21] An anaesthetist may be a pioneer at the cutting edge of anaesthetic technique but will still need the support of colleagues if involved in an adverse incident.

Nevertheless, developments in technique and drugs other than the rapid onset aminosteroids have played their part in providing alternatives to succinylcholine and indeed neuromuscular blocking agents in general. Laryngeal masks have reduced the number of patients requiring intubation for elective surgery. As anaesthetists become familiar and more confident with their use in previously forbidden territories, pioneering practice may gradually become the accepted norm and the incidence of "scoline pains" and sore throats will continue to decrease. The inroads made into ear, nose and throat anaesthesia would seem to be but one example.[22] Indeed all neuromuscular blocking agents could be used less for intubation if other non-neuromuscular block approaches to intubation became popular. The brief obtundation of airway reflexes with propofol and alfentanil,[23, 24] or even with sevoflurane[25] after gaseous induction, have attractions over blocking every skeletal neuromuscular synapse in the body.

Are there any areas where there are no safe alternatives to succinylcholine? It would be difficult to find an alternative to this drug in obstetric anaesthesia, although rocuronium has been used successfully in elective Caesarean sections.[26] Failed tracheal intubation is well documented in the obstetric population, with an incidence almost eight times higher than in other groups.[27] In the North American closed claims study, difficult tracheal intubation and oesophageal intubation comprised 23% of damaging events associated with obstetric general anaesthesia.[28] Succinylcholine provides "a gold standard" which is difficult to replace for emergency Caesarean section requiring general anaesthesia.

In other areas there are alternative options. The patient with the potential for reflux and difficult intubation would most likely be considered a candidate for awake fibreoptic intubation in North American practice rather than using succinylcholine. Mivacurium has been described as an alternative for modifying the response to ECT[29] and debate continues in the literature as to the potential benefits of rocuronium in the head injured patient with a potentially increased intracranial pressure.[30–32]

So what is the message? Succinylcholine remains a drug for trainees as it is still the only agent with a rapid onset and, importantly, rapid recovery to provide an escape route for the unanticipated difficult intubation. There are, however, few if any situations where an option is not available.

The experienced anaesthetist will make his decision based on patient safety but also on the potential morbidity and mortality associated with this depolarizing neuromuscular blocking agent.[33]

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EDITORIAL IV

Does ketorolac cause postoperative renal failure: how do we assess the evidence?

Ketorolac became available commercially in 1992, promoted as a non-steroidal anti-inflammatory drug (NSAID) with opioid-like potency. Soon after there were worrying reports of postoperative renal failure,[1–3] leaving many anaesthetists uncertain whether or not to use it and resulting in the withdrawal of the drug from some European countries. Five years later, we have more information on the benefits of ketorolac in clinical practice: should it be used more widely, selectively, or should it be withdrawn worldwide?

As with many problems in clinical practice, this can be resolved by research. But as postoperative renal failure is a rare event, the familiar randomized, controlled study is of little use. If the incidence of postoperative renal failure is assumed to be 1 in 1000 (0.1%), and we wish to know if ketorolac is associated with up to a doubling of this risk, 63 000 patients would need to be recruited![4] Even if we select a high-risk group, such as those undergoing coronary artery or major abdominal surgery (in which the incidence of renal failure is approximately 1%), we would still require more than 6000 patients.[4] Alternatively, we may choose to compare an intermediate measure of renal function, such as creatinine clearance (assuming a 25% reduction, mean creatinine clearance is 80 (SD 50) ml min^{-1}); this requires approximately 300 patients.[4] Such studies have not been done.

How can we process the range of published evidence available regarding the association between ketorolac and renal failure in order to guide our rational clinical decision-making?

Sackett and colleagues[5] have adapted several principles first elucidated by Austin Bradford Hill[6] in order to support evidence of causation. First, the different research designs are rated according to their scientific validity, or strength of association. The familiar randomized, controlled study is the best method for proving causation. But there are other designs that may have a place in anaesthesia and, in particular, the investigation of adverse events (such as renal failure) (table 1).

The least convincing form of evidence is the case series, and this includes reporting of adverse drug reactions and case reports. Here there is a *possible* association between exposure to a drug and an adverse outcome. Because they lack a denominator, we have no knowledge of incidence rate or relative risk. At most, the only use of such reports is to raise awareness and perhaps formulate hypotheses that should be tested with further research. For rare outcomes, the choice is either a case-control or cohort study.

Table 1 Evidence of causation, adapted from Sackett and colleagues[5] with permission, and Hill[6]

1. Considering each study (strength of association)	
Randomized, controlled study	++++
Cohort study	+++
Case–control study	++
Case series, case report	±
2. Considering all studies	
Consistency	+++
Temporal sequence	++
Dose–response	++
Biological plausability	+

In a case-control study, a group of patients who already have the adverse outcome is first identified ("cases") and then matched to a group of patients who do not have the adverse outcome ("controls"). The investigator then retrospectively compares the risk of the adverse outcome in those exposed to the particular drug of interest and those who were not. If this risk is significantly greater then it may be inferred that the drug causes the adverse outcome.

The best epidemiological study design is the cohort study, whereby separate groups of patients taking different drugs are followed prospectively. The incidence of ensuing adverse events is then compared between these groups and if they differ significantly, it may also be inferred that a particular drug exposure caused the outcome.

The value of these epidemiological study designs is that they are efficient, in that hundreds or thousands of patients can be analysed: all that is needed is a large database. But it must be recognized that patients are not randomized in these observational studies, and so the patient may be exposed to a drug for several reasons, which of itself may be associated with the outcome. This is known as confounding and can lead to misleading results.[5,7,8] Of equal importance are many possible sources of bias.[5,7,8] Bias and confounding should always be considered as alternative explanations to an observed relationship between drug exposure and outcome: "association does not imply causation". Epidemiological studies also provide an estimate of risk, usually presented as risk ratio or odds ratio.[5] This information can also be presented as "number needed to treat" before an adverse event (or benefit) is observed.[5,9]

When the relative strengths of these study designs are considered, all the published evidence needs to be processed: (i) is it consistent, (ii) is there a demonstrated temporal sequence between drug exposure and adverse outcome–this is particularly relevant for case-control studies and case reports, (iii) is there a dose–response relationship (greater risk if exposed to higher doses or for longer periods) and (iv) is there biological plausibility? It is the mounting body of supportive evidence that finally supports causation.[5,6]

So, does ketorolac cause postoperative renal failure? There have been isolated reports of renal failure since 1992.[1–3] There have also been several randomized, controlled studies investigating the effect of the drug on renal function,[10,11] although it should be noted that none was designed specifically to investigate the risk of postoperative renal failure. But as renal failure is such a rare complication, the randomized, controlled study is not the most reliable design (because of the risk of a false negative result). We must rely on cohort or case-control studies.[12] Unfortunately there has only been one: a post-marketing study performed by Strom and colleagues in the USA.[13] They studied 10 272 patients who received ketorolac, matched with 10 247 who received opioids, and investigated the risk of gastrointestinal and operative site bleeding. The risk (odds ratio) of gastrointestinal bleeding in those exposed to ketorolac was 1.3 (or 30% greater risk). This risk was increased in patients treated longer than 5 days and in those more than 70 yr of age (importantly, there did not appear to be an increased risk in younger patients). They also analysed the risk of renal failure and could find no added risk.[14] When all major adverse events were analysed together, there was an overall lower risk in the ketorolac group, primarily through a lower rate of myocardial infarction and respiratory complications. And so for the first time we have a reasonable estimate of risk. Therefore, this is an important and valuable study. But before accepting the conclusions of this study it must be recognized that it was not a randomized, controlled study; such epidemiological studies depend on the quality of the data, which are often collected for other reasons and so may be inaccurate or incomplete.[5 7 8]

Although there have been several case reports implicating ketorolac as a cause of postoperative renal failure, this is not supported by clinical studies (but these are few in number and inadequate in size), or by epidemiological data. Further cohort or case-control studies are required to confirm the cohort study of Strom and colleagues but none exists. Previous studies with other NSAID have demonstrated impaired renal function,[15 16] but all non-steroidal agents are not the same: they have different side effect profiles.[17] We know that renal blood flow is dependent (at least in part) on prostaglandins, especially during stressful periods in which there is activation of the renin–angiotensin system.[15 16] Hence it is plausible that ketorolac may cause renal failure. If so, we can speculate that it may be more common in patients with impaired renal blood flow, such as the elderly, those with heart failure, shock or in patients exposed to other nephrotoxic agents.[16] Currently, it remains prudent to use ketorolac cautiously in these patients (by minimizing the dose and duration of therapy) and only if persuaded by its relative benefits.

If ketorolac causes renal failure, it is a rare event. Our best estimate of incidence or risk (based on epidemiological data), is approximately 1 in 1000 to 1 in 100 000. In clinical practice this should be weighed against the many other causes of postoperative renal failure, and also the risks associated with alternative drugs or other pain control methods. As clinicians we can then process these data to determine more rationally the risks and benefits. There are gaps in our knowledge; as with all new drugs, there needs to be continued research and the most efficient method for answering these question are large, epidemiological case-control or cohort studies.

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CLINICAL INVESTIGATIONS

Ventilatory assistance and respiratory muscle activity. 1: Interaction in healthy volunteers

J. S. MECKLENBURGH AND W. W. MAPLESON

Summary

We have investigated the response of 12 normal, healthy subjects to resistance loading and ventilator assistance of spontaneous breathing. Three ventilators, the Hamilton Veolar, Engström Erica and Puritan Bennett 7200, were used to provide synchronized intermittent mandatory ventilation and two levels of pressure assistance. Total respiratory elastance and resistance were measured. The equivalent (negative) pressure of respiratory muscle activity (p_{mus}) was then calculated from measurement of flow and pressure at the mouth. With ventilatory assistance, subjects maintained frequency, decreased inspiratory time and the magnitude of p_{mus}, but increased tidal volume, thus not taking full advantage of ventilatory assistance. The waveform of p_{mus} varied in detail within and between subjects and conditions, but the all-subject mean waveforms showed for all conditions a consistency of trajectory. Increasing the level of assistance decreased the duration and hence the (negative) peak value of p_{mus}. The results suggest that some waveforms of flow or pressure from the ventilators may be more acceptable to patients than others, and that different patients may prefer different waveforms. (*Br. J. Anaesth.* 1998; **80**: 422–433)

Keywords: ventilation, spontaneous; ventilation, artificial; muscle respiratory; equipment, ventilators; measurement techniques, respiratory muscle activity

The respiratory muscles apply a waveform of force to the impedance of the respiratory system (total respiratory compliance (C) and total respiratory resistance (R)) in series with the impedance of any breathing system to which the subject is connected. If the breathing system is part of a ventilator, the ventilator applies a waveform of flow or pressure to the opposite end of the two impedances. The action of the respiratory muscles is equivalent to a waveform of (negative) generated pressure, p_{mus}, applied to the outside of the subject's thorax[1] (fig. 1). It has been shown[1] that if the subject's compliance and resistance are first measured, then the waveform of p_{mus} can be calculated from continuous measurements of flow ($\dot{v}$) and pressure at the subject's mouth (p_{mo}). Thus the combination of compliance, resistance and an appropriately applied waveform of p_{mus} constitutes a model of the respiratory system of a spontaneously breathing patient.

Previous work in this department[1] has validated a mechanical form of the model and this form is included in the models specified in BS 5724:3:12[2] for the comparative testing of ventilators in respect of their use in spontaneously breathing patients. The p_{mus} waveform specified in BS 5724:3:12 for use with the model is based on measurements made in the course of our previous work, but in only three volunteers under a limited range of conditions.

Therefore, we perceived a need to determine p_{mus} waveforms in a wider range of subjects under a wider range of conditions to assess what range of waveforms occurred and whether the waveforms could be related to characteristics of the different conditions. For practical reasons, the present study was restricted to healthy volunteers but included a range of conditions in three different ventilators.

Subjects and methods

EXPERIMENTAL DESIGN

We investigated healthy subjects while breathing air under five different conditions: (i) spontaneous breathing from atmosphere–the "unloaded" reference condition; (ii) simple resistance load, 0.5 kPa s litre^{-1} (at 1 litre s^{-1}), simulating a solely resistive breathing system; (iii) pressure assistance of 0.5 kPa, considered to be the lowest level of assistance likely to be used clinically; (iv) pressure assistance of 1.0 kPa, thought to be sufficient to completely "unload" the respiratory muscles; and (v) synchronized intermittent mandatory ventilation (SIMV) at a frequency of 6 bpm. The ventilators used were the Hamilton Veolar, Engström Elvira and Puritan Bennett 7200.

The conditions involving ventilator assistance were always applied in the same sequence: pressure assistance at 0.5 kPa, pressure assistance at 1.0 kPa and SIMV (i.e. progressively more abnormal). These three conditions were applied by each of the three ventilators to each subject–a total of nine ventilator-assisted conditions. The nine ventilator-assisted conditions were bracketed by both unloaded and resistance-loaded conditions. There were six different orders in which the three ventilators could be used and these were randomized (using computer-generated random number sequences) between

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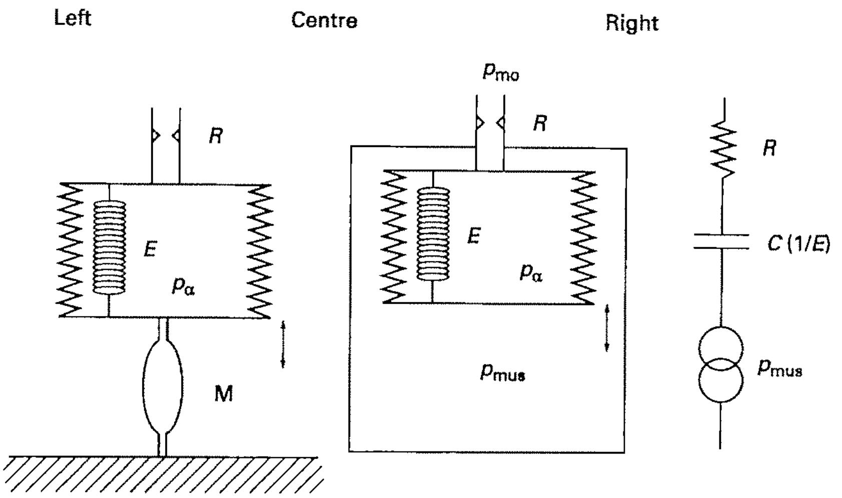

Figure 1 Left: simplified mechanical conceptual model, equivalent to the physiological reality except as follows. There is no inertance. The "alveolar" compartment is separated from the "mouth" by *R* (resistance of entire respiratory system) not just airways resistance (therefore p_a is the pressure in the "alveoli" of the model, not true alveolar pressure). Respiratory muscles (both inspiratory and expiratory) are combined in a single muscle component (M). *E* is the elastance (reciprocal of compliance) of the respiratory system. Centre: alternative model, directly equivalent to the first a waveform of negative pressure (p_{mus}) applies the same waveform of force to the base plate of the bellows as do the respiratory muscles, M. p_{mo} is the pressure at the "mouth" or airway opening. Right: equivalent electrical analogue of both models with p_{mus} represented by an ac voltage generator.

successive subjects. This pattern was applied three times, using a total of 18 subjects.

Respiratory resistance and elastance (the reciprocal of compliance) were estimated from periods of continuous mandatory ventilation (CMV) at the beginning and end of the experimental sequence. The ventilator used for CMV runs in any one subject was the one in the middle of the random order of the ventilators for that subject.

EXPERIMENTAL PROCEDURE

After obtaining approval from the relevant Research Ethics Committee and written informed consent, we studied subjects, aged 18–50 yr, not suffering from any disease. It was essential that subjects could relax their respiratory muscles completely during a period of CMV for determination of elastance and resistance. During trial CMV runs, acceptable subjects showed a mouth pressure pattern with no negative phases, a steady increase in pressure during the inspiratory phase and a similar pattern in every breath.

The experimental sequence consisted of 15 runs, with the subject seated: CMV, unloaded, loaded, the nine ventilator-assisted conditions, loaded, unloaded and CMV. For each run, the subject breathed under the specified conditions via a sensing manifold, for a total of 4 min (2 min for acclimatization and 2 min for recording). This was followed by 2 min of recovery, breathing room air directly. All symptoms of inadequate technique (e.g. leaks from the mouth piece, swallowing, breath-holding and airway restriction during inflation) were noticeable on a "rolling" display during the acclimatization and recording periods, and instructions were given to try to correct such inadequacies.

End-tidal carbon dioxide partial pressure ($P\text{E}'_{CO_2}$) was monitored. The run was terminated if hyperventilation caused $P\text{E}'_{CO_2}$ to decrease to 3 kPa.

SETTING OF THE VENTILATORS

For the CMV runs, frequency was initially set to 15 bpm with an inspiratory to expiratory (I:E) ratio of 1:2, and a tidal volume of approximately 1.5 times the spontaneous tidal volume recorded during the trial runs. The inspiratory flow pattern of the ventilators was set to "sine-wave" (or the nearest approximation to it in the Engström Elvira–"increasing flow"). The initial frequency, I:E ratio and tidal volume were adjusted until subjects were comfortable and best able to suppress normal respiratory activity. A degree of hyperventilation and hence hypocapnia was aimed for to reduce respiratory drive and make relaxation easier for the subject.

The different ventilators were connected initially to a bellows lung model (Medishield) with a compliance of 0.5 litre kPa^{-1} and resistance of 0.5 kPa s litre^{-1}, and the controls adjusted to give, as closely as possible, the same levels of pressure assistance. These settings of the controls were noted and used in all subjects.

In the SIMV runs, frequency was set to 6 bpm and the other inflation characteristics were initially set as in the initial CMV runs for each subject. However, tidal volume and duration of the inspiratory phase or amplitude of the inspiratory flow waveform were sometimes adjusted at the request of the subject.

A standard Intersurgical breathing system was used throughout. It consisted of a Y-piece and two 1.8-m lengths of corrugated polyethylene tubing. In all ventilators the display and control of "airway" pressure was based on sensing the breathing system pressure within the ventilator.

INSTRUMENTATION

The sensing manifold consisted of a mouth piece, followed by a heat and moisture exchanger and filter (HMEF) (Portex Humid Vent), a T-piece for mouth pressure measurement, a screen pneumotachograph for flow measurement and a T-piece for extracting a

200-ml min^{-1} sampling flow of gas for end-tidal carbon dioxide measurement.

Pressure was measured by a strain-gauge differential pressure transducer (Pioden type UP) driven by a conditioning amplifier (Analog Devices Strain-gauge Amplifier 1B31). Flow was measured by a screen pneumotachograph (Mercury Electronics C100) and differential pressure transducer (Valodyne MP45) driven by a conditioning amplifier (P. K. Morgan pressure transducer monitor). End-tidal carbon dioxide partial pressure was monitored using a Datex Capnomac Ultima multi-gas analyser which was calibrated with a certified gas mixture (5% carbon dioxide in air; BOC Ltd) before and after measurements in each subject.

Pressure and flow calibration was by reference to a Timeter RT200 calibration analyser verified to National Accreditation of Measurement and Sampling (NAMAS) standards by Universal Calibration Ltd. The pneumotachograph was calibrated with dry air; therefore inspiratory flows in the ventilator-assisted runs would be correct. In the unassisted runs, when room air was inspired, the effect of ambient humidity reduced the viscosity of air so producing an error of approximately −0.3% in inspired flow, which was ignored.

The sensitivity of the pneumotachograph in the expired direction was not measured directly. As the conditions during expiration were different and unknown, an empirical calibration factor was calculated so that the drift in end-expired volume was eliminated from the recording as a whole, but breath-to-breath variations were preserved. Thus all flows and volumes are expressed at ambient conditions, ATPD.

The resistances of the sensing manifold and the resistance load (a 7-mm diameter orifice) conformed to the equations $\Delta p=0.188\ \dot{v}$ and $\Delta p=0.514\ \dot{v}^2$, respectively, where Δp=pressure difference across the manifold or load in kPa and $\dot{v}$= flow in litre s^{-1}.

The internal volume of the sensing manifold was 144 ml, 45 ml being within the HMEF. In the unassisted runs a short tube of 15 ml internal volume was added to the open end of the manifold to match approximately the dead space of the Y-piece of the ventilator breathing system. In the resistance-loaded, unassisted runs, the tube incorporated the 7-mm diameter orifice. Thus there was comparable rebreathing in all runs.

Pressure and flow data were captured using an interface board (MIO-16-25, National Instruments), microcomputer (Apple Macintosh IIcx running system 7.1) and data acquisition software (LabView ver. 2, National Instruments), and stored on magnetic disk.[5]

ESTIMATION OF ELASTANCE AND RESISTANCE FROM CMV RUNS

Elastance (E) and resistance (R) were estimated using a multiple regression method.[1] Initially, separate estimates were made for the inspiratory and expiratory phases of each breath. The breaths were then ranked on the basis of each of three variables: inspiratory–expiratory differences in elastance (1) and in resistance (2), and residual SD of the regression fit (3). Good relaxation was indicated by small differences and small SD values.

The chosen cut-off point (a rank of <500 for all three ranked variables) yielded 310 acceptable breaths of the original 836 (37%). To maintain the balance of the experimental design, even with two examples of each of the six sequences of the three ventilators, would have involved including one subject with no acceptable breaths. The best compromise that could be obtained was a set of 12 subjects which included only one example of one sequence and three examples of another. Therefore, the balance of the experimental design was upset, but all subjects had at least 10 breaths with satisfactory relaxation.

In each of the 12 selected subjects, those breaths from the CMV run at the end of the experimental sequence which had shown "good relaxation" were re-submitted to regression analysis, but single estimates of resistance and elastance were obtained for each whole breath (rather than separate estimates for each phase). In this way, breath-by-breath estimates of resistance, elastance and residual variance of the regression were obtained for each of the 12 selected subjects. The reciprocal of the residual variance for each breath was used to calculate weighted means[4] of resistance and elastance for each subject.

CALCULATION OF P_{mus} WAVEFORM IN THE MAIN EXPERIMENTAL RUNS

The waveforms of mouth pressure, flow and volume from the main experimental runs were processed continuously for each 2-min recording to give waveforms of p_{mus}. This was done by using the equation in appendix 1.

$$p_{\text{mus}}=p_{\text{mo}}-(P_{\text{moE}'}-R\dot{v}_{\text{E}'})-R\dot{v}-Ev+P_{\text{musE}'}$$

where p_{mo}=mouth pressure, $\dot{v}$=flow (positive for inspiration), v=volume of gas in the lungs relative to a reference level, and $P_{\text{moE}'}$, $P_{\text{musE}'}$ and $\dot{v}_{\text{E}'}$=the end-expiration values of p_{mo}, p_{mus} and $\dot{v}$, respectively (see below). The unknown $P_{\text{musE}'}$ in the equation was assumed to be zero, so that the shape of the p_{mus} waveform could be obtained, but there is uncertainty over the true zero.

EXTRACTION OF NUMERICAL RESPIRATORY VARIABLES FROM THE WAVEFORMS OF FLOW, VOLUME, MOUTH PRESSURE AND P_{mus}

From each breath in each experimental run (other than the CMV runs), 14 variables were obtained (volume in litre and ventilation in litre min^{-1} (both ATPD), pressure in kPa, time in s, frequency in bpm):

V_{T}=inspired tidal volume.

T= respiratory period (from the start of inspiratory flow in one breath to the start of inspiratory flow in the next).

f=60/T.

T_{I}=inspiratory time (from the start of inspiratory flow to the start of expiratory flow).

T_{E}=expiratory time ($T-T_{\text{I}}$).

T_{c}=contraction phase time of the p_{mus} waveform (time from the start of the inspiratory effort to the peak).

$\dot{V}$=total ventilation ($V_T\ f$). (This is calculated for each individual breath so that the mean is not equal to mean V_T×mean f.)

$\dot{v}$=instantaneous flow (inspiratory direction positive).

$P_{mo\ pk}$=peak magnitude of a "smoothed" (rolling average of three points) waveform of mouth pressure (negative in unassisted conditions) during the inspiratory flow phase.

$P_{mo\ mn}$=mean value of mouth pressure over the inspiratory flow phase.

$P_{mus\ pk}$=peak negative value of a "smoothed" (as for $P_{mo\ pk}$) waveform of p_{mus}.

P_{trg}=most negative mouth pressure occurring in the 0.3 s before the start of inspiratory flow.

$P_{moE'}$ (PEEP)=end-expired mouth pressure derived from the mean pressure over the 0.2 s period ending 0.15 s before mouth pressure becomes negative before the next breath.

$P_{musE'}$=value of p_{mus} at end-expiration, derived using the same time window as used for $P_{moE'}$ (PEEP).

$\dot{v}_{E'}$=value of flow at end-expiration, derived using the same time window as used for $P_{moE'}$ (PEEP).

The time windows used to determine P_{trg}, $P_{musE'}$, $\dot{v}_{E'}$ and PEEP were based on inspection of many overlay recordings.

For each variable, except $P_{E'CO_2}$, mean values for all breaths in each run were calculated before statistical analysis. Mandatory and spontaneous breaths in the SIMV condition were averaged separately. The mean $P_{E'CO_2}$ for each run was taken as the average of the pair of values at the beginning and end of each 2-min run. Therefore, this mean $P_{E'CO_2}$ applied to both mandatory and spontaneous breaths in the SIMV condition.

Four factors pertained to each run: for the unassisted runs–(1) subject (1–12), (2) condition (unloaded and resistance-loaded), (3) occasion (before and after the ventilator-assisted runs) and (4) last (the last ventilator in the sequence of ventilator-assisted runs (relevant only to the "after" runs); and for the ventilator-assisted runs–(1) subject (1–12), (2) condition (pressure assistance at 0.5 kPa and 1.0 kPa and mandatory and spontaneous breaths in SIMV), (3) ventilator (Hamilton Veolar, Engström Elvira and Puritan Bennett 7200) and (4) serial position (the position of the ventilator in the sequence of ventilator-assisted runs, 1–3).

In the case of the unassisted runs, the factor "last" was included because it was anticipated that the characteristics of the ventilator used last might have an effect on the "after" runs of unassisted breathing.

Two-way and three-way mixed-effect analyses of variance (ANOVA) and *t* tests were performed on the numerical data using the Minitab statistical package (version 8.1 running on various models of Apple Macintosh using system 7.1 or 7.5). As this study was exploratory in nature and not a definitive clinical trial, a fixed P=0.01 was used as the threshold for significance, partly as a token recognition of the large number of comparisons performed, but primarily to provide an internally consistent threshold for selecting differences in the variables for comment.

AVERAGING OF P_{mus} WAVEFORMS

A complex averaging process which preserved the shapes of the waveform (appendix 2) yielded a mean "contraction" phase waveform (from the start to the peak of p_{mus}) and a mean "relaxation" phase waveform (from the peak onwards) for each subject in each condition.

In the SIMV condition, the waveforms of p_{mus} for the mandatory and spontaneous breaths were very different and were therefore averaged separately. Thus the original three ventilator-assisted conditions became four, for each of the three ventilators. Together with the four, bracketing, unassisted conditions, this gave a total of 16 average waveforms for the contraction and relaxation phases, for each of the 12 subjects. The 12 subject waveforms were similarly averaged for each condition to produce overall mean waveforms, for each phase for each condition.

Results

We recruited 21 subjects; two were unable to relax during the trial period of CMV and one subject fell asleep, producing an erratic breathing pattern during one of the runs. The remaining 18 subjects satisfactorily completed the experimental procedure, each producing 2-min recordings from each of 15 runs. Of these 18 subjects, 12 provided good estimates of elastance and resistance.

ESTIMATES OF ELASTANCE AND RESISTANCE

In the 12 selected subjects (10 males, two females), mean age was 26.7 (range 20–44) yr, mean height 1.81 (SD 0.11) m, mean weight 74.4 (10.1) kg, with total respiratory elastance of 1.13 (0.21) kPa litre^{-1} and resistance of 0.56 (0.12) kPa s litre^{-1}. The 95% confidence limits for elastance and resistance in individual subjects were all within ±12%, mostly within ±5%.[3]

As the remainder of the results depend on the validity of these estimates, it is worth noting that mean elastance (1.13 kPa litre^{-1}) was close to the values of Altman and Dittmer[5] and Diem and Lentner[6] (both 1 kPa litre^{-1}) and to the geometric midpoint (1.04 kPa litre^{-1}) of the range (0.54–2.0 kPa litre^{-1}) given by Cotes[7] for the sum of lung and chest wall elastance. Mean resistance (0.56 kPa s litre^{-1}) included resistance of the HMEF and mouth piece (0.16 kPa s litre^{-1}). Therefore, mean total respiratory resistance for comparative purposes was 0.40 kPa s litre^{-1}. This is approximately 50% greater than the total respiratory resistance given by Cotes (0.26 kPa s litre^{-1}) but is in agreement with that of Diem and Lentner (0.396 kPa s litre^{-1}).

MEAN RESPONSE TO THE DIFFERENT VENTILATORY CONDITIONS

Numerical variables

Table 1 compares the mean values for the different conditions for each numerical variable. PEEP and triggering pressure (P_{trg}) are omitted because, in the unassisted runs, the former is zero and the latter is irrelevant.

Table 1 Comparison of all conditions for numerical variables (volumes expressed at ATPD). Mean of all subjects for each condition for nine variables, where the value for each subject was the mean for the two occasions (before and after) or the three ventilators. Also, *P* values from the two-way ANOVA (subject by condition–55 df) and from paired *t* tests of the differences from the unloaded condition (11 df). PA=Pressure assistance, SIMVm=mandatory breaths in SIMV, SIMVs=spontaneous breaths in SIMV

	Tidal volume (litre)			Frequency (bpm)			Ventilation (litre min^{-1})		
Condition	Mean	Mean difference (%)	*P* by *t* test	Mean	Mean difference (%)	*P* by *t* test	Mean	Mean difference (%)	*P* by *t* test
Unloaded	0.711			12.67			8.54		
Res. loaded	0.756	6	0.072	11.75	−7	0.004	8.31	−3	0.110
PA 0.5 kPa	0.974	37	0.006	12.42	−2	0.730	11.50	35	0 003
PA 1.0 kPa	1.082	52	≤0.001	13.23	4	0.430	13.58	59	≤0.001
SIMVm	0.842	18	≤0.001	13.86	9	0.100	11.54	35	≤0.001
SIMVs	0.693	−3	0.580	13.58	7	0.170	9.91	16	0.008
P by ANOVA	≤0.001			0.003			≤0.001		

	Inspiratory time (s)			Contraction phase time (s)			End-tidal $P\text{co}_2$ (kPa)		
Condition	Mean	Mean difference (%)	*P* by *t* test	Mean	Mean difference (%)	*P* by *t* test	Mean	Mean difference (%)	*P* by *t* test
Unloaded	2.10			1.78			5.39		
Res. loaded	2.36	13	≤0.001	1.97	10	0.007	5.30	−2	0.120
PA 0.5 kPa	1.63	−22	≤0.001	1.45	−19	0.014	4.43	−18	≤0.001
PA 1.0 kPa	1.40	−33	≤0.001	1.09	−39	0.001	3.91	−27	≤0.001
SIMVm	1.46	−31	≤0.001	1.23	−31	0.001	4.55	−16	≤0.001
SIMVs	1.85	−12	0.013	1.54	−13	0.024			
P by ANOVA	≤0.001			≤0.001			≤0.001		

	$P_{\text{mus pk}}$ (kPa)			$P_{\text{mo con}}$ (kPa)			$P_{\text{mo pk}}$ (kPa)		
Condition	Mean	Mean difference (%)	*P* by *t* test	Mean	Mean "actual" difference	*P* by *t* test	Mean	Mean "actual" difference	*P* by *t* test
Unloaded	−0.953			−0.009			−0.016		
Res. loaded	−0.990	−4	0.350	−0.075	−0.066	≤0.001	−0.132	−0.116	≤0.001
PA 0.5 kPa	−0.814	15	0.170	0.400	0.409	≤0.001	0.629	0.645	≤0.001
PA 1.0 kPa	−0.623	35	0.004	0.754	0.763	≤0.001	1.064	1.080	≤0.001
SIMVm	−0.751	21	0.005	0.369	0.378	≤0.001	0.773	0.789	≤0.001
SIMVs	−0.884	7	0.200	0.042	0.051	≤0.001	0.215	0.231	≤0.001
P by ANOVA	≤0.001			≤0.001			≤0.001		

The first column for each variable gives the mean value for each of the six conditions. Two-way ANOVA (condition by subject, with subject as a random variable) of the mean values for each subject showed significant differences between conditions for all variables (*P* always ≤0.003 in the first column of table 1). As the interest is in the comparison with normal, unloaded, unassisted breathing, the remaining columns for each variable show percentage differences for the other conditions, and *P* values by *t* test for each difference.

Resistance loading led to an increase in contraction phase time, and in inspiratory time, with a decrease in frequency, and slightly more negative mouth pressures. Other changes were not significant but formed a pattern consistent with the above changes: an increase in the (negative) magnitude of $P_{\text{mus pk}}$ and an increase in tidal volume which, with the matching decrease in frequency, led to little change in ventilation or $P\text{E}'_{\text{CO}_2}$.

In the ventilator-assisted conditions, there were large increases in $P_{\text{mo pk}}$ with lesser decreases in the magnitude of $P_{\text{mus pk}}$. Consequently, tidal volume increased markedly, especially with pressure assistance (PA): 37% and 52% for 0.5 and 1.0 kPa PA, respectively. In the SIMV runs, mandatory tidal volume was deliberately set to the high value found most appropriate for determination of elastance and resistance of subjects (in the CMV runs). Yet subjects did not take advantage of this to reduce tidal volume of spontaneous breaths in SIMV (SIMVs) compared with unloaded, unassisted breathing.

The reduction in inspiratory time in the ventilator-assisted conditions was marked (12% to 33%) and similar to the reduction in duration of the contraction phase of the p_{mus} waveform (14% to 39%). The reduction was significant in all conditions except for spontaneous breaths in SIMV.

The increases in ventilation (35–59%) and the corresponding decreases in $P\text{E}'_{\text{CO}_2}$ (16–27%) reflected the increases in tidal volume with only small changes in frequency. The increases also illustrated that despite considerable reductions in $P_{\text{mus pk}}$, subjects did not take full advantage of the assistance provided by the ventilators.

Waveform of p_{mus}

Contraction phase. For the contraction phase, figure 2 shows for each subject, the mean of the unassisted, unloaded condition before (solid line) and after (dotted line) the sequence of ventilator-assisted runs and the overall mean (and confidence limits) of the 24 waveforms for those two occasions–the "reference" mean waveform. Figure 3 shows, for each of the 14 combinations of condition and ventilator, the all-subject mean waveforms (solid lines), with confidence limits, overlaid with the mean reference waveform.

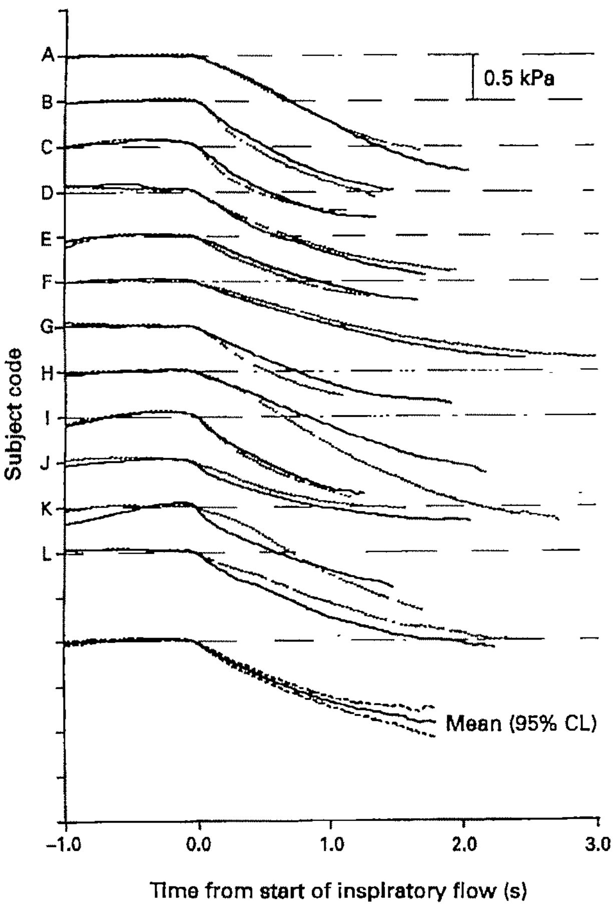

Figure 2 Mean contraction phase waveform of p_{mus} for each subject for the unassisted, unloaded condition before (solid line) and after (dotted line) the sequence of ventilator-assisted runs and the overall mean and 95% confidence limits (CL) (broken line) of the 24 waveforms for these two occasions–the "reference" mean waveform. The waveforms are synchronized to the start of inspiratory flow. The waveforms of the subjects (A– L) are offset from one another, the zero for each waveform being indicated by a faint line at the level of each identification label.

The trajectories of the waveforms are essentially the same in all conditions: the reference waveform is almost always entirely within the confidence limits. However, the durations, and hence amplitudes, differ between conditions.

Relaxation phase. For the relaxation phase, a similar procedure was followed, but with the 24 mean "before" and "after" waveforms (fig. 4) individually time-shifted to a midway "synchronization" point (appendix 2) so that there is no common time reference (hence the 1-s time bar, instead of a time scale). The overall mean, the relaxation phase reference mean waveform is also shown.

Figure 5 shows, for each of the 14 combinations of condition and ventilator, the all-subject mean waveforms (with confidence limits (CL)) overlaid with the relaxation phase reference mean waveform.

As in the contraction phase, the trajectory is essentially the same for all conditions (the "reference" mean waveform lies almost entirely within the confidence limits for each condition) but the durations differ. The duration of the phase up to the most positive value (as plotted in fig. 5) is lengthened by resistance loading and shortened by SIMV and, in the PB 7200, by pressure assistance. For conditions where the relaxation phase is short, the waveform coincides with the later part of the mean reference waveform.

RESPONSE TO INDIVIDUAL VENTILATORS AND OCCASIONS

Numerical variables

Three-way ANOVA was used to assess the effect of the series of ventilator runs on the unassisted conditions. The three factors were "occasion" (before *vs* after), "condition" (unloaded *vs* loaded) and "subject" (the last as a random variable). The only significant change from before to after the ventilator-assisted runs was an 8% reduction in $P\text{E}'_{CO_2}$ (P=0.008) (table 2) and there were no significant interactions between occasion and condition, that is the effects of adding a resistance load were similar before and after the ventilator-assisted runs.

Another three-way ANOVA (condition, ventilator, subject) revealed significant differences between ventilators for some variables and significant ventilator–condition interactions (P for "differences between runs") for a different set of variables (table 3). For each variable, the least significant difference (lsd)[8] for P=0.01 between ventilators allows identification of which systematic differences between ventilators led to overall significance, and the between-run lsd allows identification of differences between ventilators which are significant only in particular conditions. This leads to the following qualitative summary of table 3.

Two variables are determined almost entirely by ventilator design: PEEP, which was consistently low in the PB7200, and P_{mg}, which was consistently high in the Veolar and low in the Elvira, especially in SIMVs. Other variables depended partly on how the operator set the ventilators: nominally the same for all three for $P_{mo\ pk}$ in pressure assistance, but in accord with what "suited" the subject in terms of tidal volume and inspiratory time in SIMV. Contraction phase time and $P_{mus\ pk}$ depended on how the subjects reacted to each ventilator–condition combination. Finally, tidal volume, frequency and total ventilation were consequences of the values of all of the other variables.

Differences between ventilators in particular conditions were as follows. In SIMV (both the mandatory and spontaneous breaths), the Elvira produced (compared with the Veolar and PB 7200) large values of $P_{mo\ pk}$ (and $P_{mo\ mn}$), small values of inspiratory time and $P_{mus\ pk}$, and large values of frequency and total ventilation, with no significant differences in tidal volume. In pressure assistance, the PB7200 produced small values of inspiratory time and $P_{mus\ pk}$, large values of frequency and, compared with the Veolar, small values of tidal volume, with generally no significant difference for total ventilation.

A final three-way ANOVA used the "position" of the ventilator in the sequence of three, rather than the type. This revealed some acclimatization to the ventilator-assisted runs: from the mean for the first exposure to the four conditions to the mean of the means for the second and third exposures, tidal volume decreased by 10%, ventilation by 5% and $P_{mus\ pk}$ by 20%.

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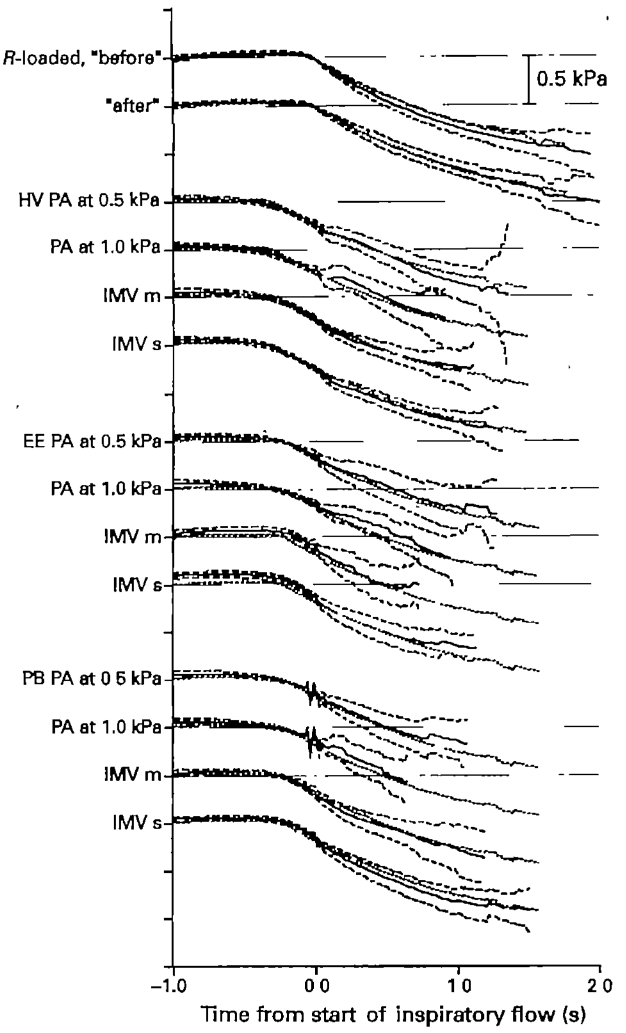

Figure 3 All-subject mean contraction phase waveform of p_{mus} (solid line) for the resistance-loaded and ventilator-assisted conditions with 95% confidence limits (CL) (broken line), overlaid with the overall mean waveform for the unloaded, unassisted condition (the "reference" mean waveform of figure 2–dotted line). For the ventilator-assisted conditions, the reference waveform has been time-shifted to match the waveforms for each ventilator. The same shift has been used for all four conditions in each ventilator. The time shifts are reflected in the different times at which the dotted waveforms end. The zero for each waveform is indicated by a faint line.

p_{mus} *waveform*

There were no striking systematic differences in mean waveform (figs 3, 5) between the sets for different ventilators, or between occasions (before or after the ventilator runs) for a resistive load.

RESPONSE OF INDIVIDUAL SUBJECTS

Numerical variables

In all three types of ANOVA, the differences between subjects were significant (compared with the residual, ventilator–condition–subject interaction mean square) for all variables except P_{mo}. This was broadly to be expected: subjects differ from one another, and P_{mo} was zero, or near zero, in the unassisted runs and set to the same nominal 0.5 or 1.0 kPa in pressure assistance. Only in the mandatory breaths of SIMV did P_{mo} depend on the response of the patient to a preset tidal volume.

Although subjects differ from one another, they might be expected to respond consistently to changes in load or assistance. Simple graphs for each variable, with a line for each subject,[3] showed that the subjects responded consistently to the resistance load, but showed variable after-effects of the sequence of ventilator-assisted runs. Also, in the ventilator-assisted runs there were significant subject–ventilator interactions for all variables except the largely ventilator-controlled P_{mo}.

The spread of responses between subjects was generally similar for all three ventilators and for all variables, except P_{mg}. This was much more consistent between subjects, but less so in the Veolar or Elvira than in the PB7200, despite the sensitivity within each ventilator being set the same for all subjects.

p_{mus} *waveform*

For each ventilator–condition combination, there was variation between subjects in the shape of the p_{mus} waveform in both the contraction and relaxation phases. In some combinations the variation was slight; in others very marked.[3] Despite these wide variations, the mean waveforms for all subjects were, for all conditions, similar in trajectory to the reference waveforms (figs 3, 5).

Discussion

AVERAGE RESPONSE OF P_{MUS} TO DIFFERENT CONDITIONS

One striking feature of the results is that our subjects, on average, preserved the trajectory of the waveform of p_{mus} but changed the duration of the contraction phase, and hence the amplitude of p_{mus}, in response to the different conditions (fig. 3).

The other method by which p_{mus} amplitude could be changed would be to maintain the duration of the contraction phase but change the slope of the trajectory of p_{mus}. This occurred occasionally in four subjects: in some ventilator-assisted conditions the trajectory became much less steep soon after the start of inspiratory flow. On the other hand, in three subjects, the slope actually increased in similar conditions, leading to the essentially constant average trajectory for all conditions.

Resistance loading increased the contraction phase time (table 1), matching the increased inspiratory time reported by Milic-Emili and Zin[9]; on the other hand, pressure assistance and SIMV decreased contraction phase time. In SIMV, this applied to both spontaneous and mandatory breaths. Corresponding changes occurred in relaxation phase time: resistance loading extended the early part of the relaxation phase leading to a decrease in frequency with load; pressure assistance and SIMV truncated the early part of the relaxation phase (fig. 5) but increased the "pause" part of the phase (after p_{mus} had reached its most positive value) leading to small, non-significant changes in frequency.

Thus the changes were in the expected direction and, with the resistance load, of a magnitude sufficient to maintain alveolar ventilation (negligible change in $P\mathrm{E}'_{\mathrm{CO_2}}$) (table 2). This is in accordance with the classical response to resistance loading.[9] However, the second striking feature of the results is that in pressure assistance and SIMV, the changes were generally inadequate to compensate for the assist-

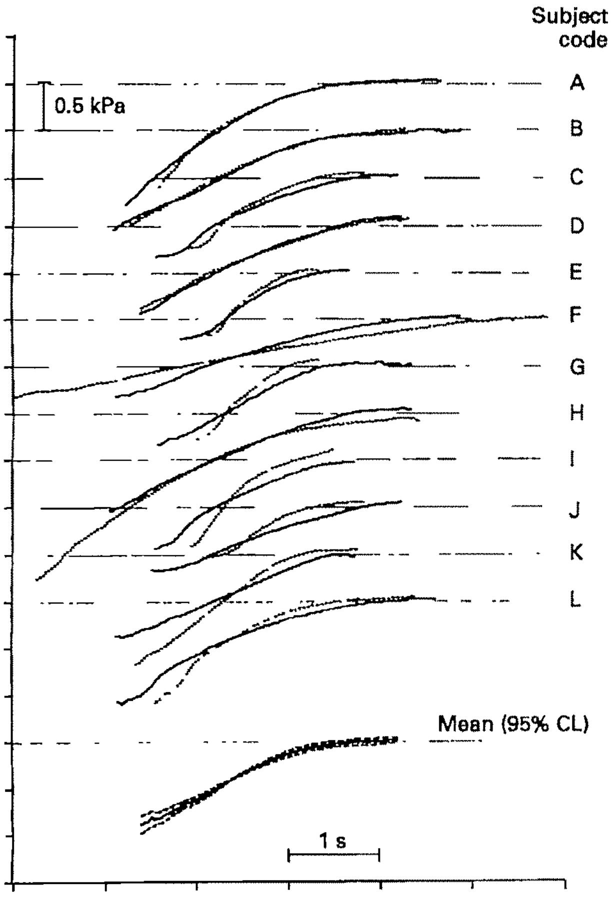

Figure 4 Mean relaxation phase waveform of p_{mus} for each subject for the unassisted, unloaded condition before (solid line) and after (dotted line) the sequence of ventilator-assisted runs and overall mean waveform and 95% confidence limits (CL) for these two occasions–the relaxation phase "reference" mean waveform. Time shifts have been applied to each before and after waveform so that the synchronization points (the times when a polynomial fitted to each waveform reached 0.75 of the amplitude of the smallest of the 24 waveforms) are all vertically aligned. The zero for each waveform is indicated by a faint line.

ance; consequently, ventilation increased substantially. There were exceptions: in some subjects, with pressure assistance at 1.0 kPa, the contraction phase ended almost immediately inspiratory flow began, and there were several instances of the phase ending within 0.5 s. Thus some subjects took advantage of the assistance to reduce the work done by the inspiratory muscles; on the other hand, the three subjects who increased the slope of their p_{mus} trajectory in the contraction phase actually increased the work done during ventilatory assistance.

It remains that, on average, the reduction in p_{mus} was much less than that needed to maintain normal ventilation.

POSSIBLE REASONS FOR LIMITED REDUCTION IN P_{MUS} WITH ASSISTANCE

The limited reduction in p_{mus} with ventilatory assistance is difficult to explain: the resulting increase in ventilation reduced $P\text{E}'_{CO_2}$ (to <4 kPa with 1.0 kPa of pressure assistance) which would be expected to reduce respiratory drive.

Being connected to a ventilator is not a natural state and it may be that considerable time is required for subjects to become accustomed to assisted ventilation, if they ever do. The fact that ventilation decreased only 10% between measurements with the first ventilator in the sequence and those with the second and third, supports this possibility.

Another factor is that it may have been an instinctive response to minimize the unusual feeling of positive pressure in the lungs and this may be the reason for the increased slope of the p_{mus} trajectory in three subjects. All subjects had experienced this positive pressure during the period of CMV for estimation of elastance and resistance, but only three were well accustomed to the experience from preliminary studies and only two of these greatly reduced their contraction phase time and hence p_{mus} amplitude.

A third factor is that the request to each subject to "breathe normally" may have been interpreted as an instruction to maintain the normal p_{mus} waveform rather than the expectation, which was to maintain normal ventilation.

Finally, it may be that, even if subjects wanted to maintain the same ventilation, they did not know how to do so, except with the resistance load. They would all be familiar with resistance to breathing, from upper respiratory tract infections, whereas most of them had no experience of ventilator assistance.

EVIDENCE OF CHANGES IN P_{MUS} IN OTHER STUDIES

The only study to measure p_{mus} in the manner described here[10] gave no information on the change in p_{mus} with ventilatory assistance. However, several surrogate measures have been used: motor–nerve input to respiratory muscles,[11] integrated EMG[12–14] and oesophageal pressure.[15] [16] It is interesting to see how the responses vary between different circumstances.

Response to assistance

In this study, subjects were breathing at only a small fraction of their maximum breathing capacity so that ventilatory assistance was superfluous. However, when the maximum breathing capacity is reduced to near the current level of ventilation, or when the ventilatory demand is increased (e.g. by exercise) towards the maximum breathing capacity, assistance might be more welcome.

One study[16] measured oesophageal pressure in five patients with chronic obstructive airways disease; applying triggered nasal pressure assistance decreased the peak p_{oes} by 80%. Unfortunately, it is not possible to tell if the reduction was caused by a change in duration or a change in slope of p_{oes}.

The complementary circumstance was investigated[15] by measuring oesophageal pressure in four volunteers who were exercising to 80% of their maximum breathing capacity. Providing assistance to these subjects roughly halved the pressure–time integral of p_{oes}. In two subjects, this was achieved by a reduction in the duration of the contraction phase with no change in trajectory; in the other two, the trajectory started in the same manner in each breath, but subsequently flattened, with no change in the duration of the contraction phase.

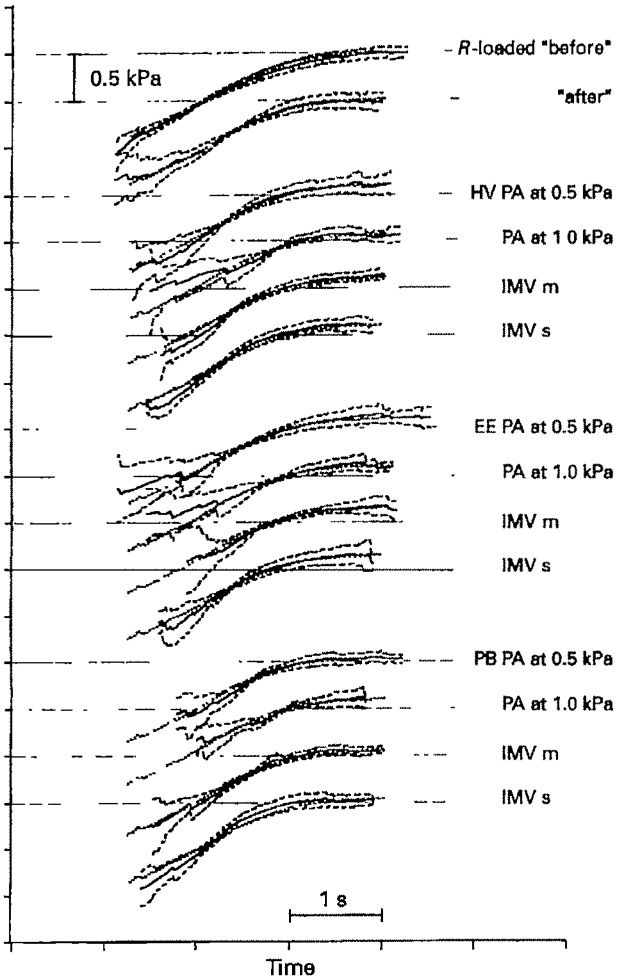

Figure 5 All-subject mean relaxation phase waveforms of p_{mus} (solid line) for the resistance-loaded and ventilator-assisted conditions with 95% confidence limits (broken line). Each waveform is terminated at its most positive value (that the waveform subsequently returned to zero can be seen in fig. 3) and is overlaid with the relaxation phase "reference" mean waveform of figure 4 (dotted line). In each case the reference waveform has been pressure-shifted to match the pressure at the end of each of the 14 mean waveforms. The mean waveforms have then been time-shifted, relative to the (time-fixed) reference waveform, so that each is coincident with the reference waveform at its synchronization point (see caption to fig. 4).

Response to load

In this study, the resistive load (0.5 kPa s litre^{-1}) was approximately equal to the total respiratory resistance (0.4 kPa s litre^{-1}) and subjects responded by a small increase in contraction phase duration with no change in slope. However, as might be expected, when the load is much greater, the slope increases: when a resistive load was imposed on ponies[14] (approximately 40 times the normal total respiratory resistance of a pony[17]) a very large increase in slope resulted.

The ultimate load is total occlusion and when, in anaesthetized animals[11] and humans,[12 13] the airway was suddenly occluded at the end of one expiration, the integrated EMG at the next "breath" followed the previous trajectory for a greater duration.

POSSIBLE CONTROL MECHANISMS

Two possible control mechanisms are clearly not supported by the present data. First, response of the respiratory centre to metabolic input is contradicted by the marked decrease in end-tidal, and hence arterial, $P\text{co}_2$ during (table 1) and after (table 2) ventilator-assisted runs. Second, if the γ-motor drive of the spindle reflex (the primary load-compensation mechanism of skeletal muscle) operated in the respiratory muscles in the circumstances of the present study, it would lead to changes in the slope of the p_{mus} waveform, not in its duration.

Table 2 Effect of "hangover" of the ventilator-assisted runs on the "after" unassisted runs: mean values for all subjects for each condition on each occasion of the unassisted runs for end-tidal $P\text{co}_2$ (kPa). Marginal means together with *P* values and standard errors of the differences (SED) between occasions, between conditions and between runs from mixed-effect ANOVA

Condition	Occasion Before	After	Means	Differences between conditions (df=11) *P* (SED)
Unloaded	5.62	5.16	5.39	0.118
Resistance loaded	5.53	5.07	5.30	(0.052)
Means	5.58	5.11	5.34	
Diffs between:	Occasions (df=11)		Runs (df=11)	
P	0.008		0.943	
SED	0.144		0.081	

Other possible control mechanisms include the response of the respiratory centre to proprioceptive inputs from muscles, tendons, joints and lung tissue. Such proprioceptive information could modify the output of the respiratory centre over several breaths or it could lead to immediate, and even within-breath, modification. To determine the relative importance of longer-term compared with immediate control requires studies where the load or assistance is varied within a single breath or between adjacent breaths, and where monitoring is continuous, whereas our study did not record the immediate effects of the various imposed conditions, only the relatively steady-state responses after 2 min of acclimatization.

The classical Hering–Breuer inspiratory-off reflex can be stated as: inspiratory effort is terminated at a time that is dependent on the volume inhaled and on the rate of increase of volume.[10] Our results are consistent with this to the extent that the contraction phase was shortened during assistance, even though not enough to compensate. However, it is not possible to determine if the response is the result of lung stretch receptors (the classical Hering–Breuer inputs) or a slow integrative adaptation of the respiratory centre output in response to a variety of neural and metabolic inputs.

Although this study does little to discriminate between different possible control mechanisms, the results include novel features which need to be explicable by any universal theory of respiratory control.

INDIVIDUAL FEATURES OF THE VENTILATORS

Some features of the p_{mus} waveform can be attributed to characteristics of a particular ventilator. The oscillation in the PB7200 waveform during pressure assistance (fig. 3) occurred with all subjects. It can be explained in terms of the rapid pressure oscillations generated by the PB7200 at the start of a pressure-assisted breath corrupting the calculated p_{mus} waveform.[3]

The Elvira in SIMV and the PB7200 in pressure assistance demonstrated a pattern of anomalous behaviour. These ventilator–condition combinations were associated (table 3) with smaller values of p_{mus}, shorter contraction phase times and higher frequencies than with the other ventilators for each of those conditions. In pressure assistance, it is mouth pressure that is controlled by the ventilator. How-

Table 3 Comparison of ventilators with classification by type: mean values for all subjects for each condition with each ventilator for nine variables. Marginal means together with P values and the least significant difference (lsd)[a] for P=0.01. HV=Hamilton Veolar, EE=Engstrom Erica, PB=Puritan Bennett 7200, PA=pressure assistance, SIMVm=mandatory breaths in SIMV, SIMVs=spontaneous breaths in SIMV

	Ventilator				
Condition	HV	EE	PB	Means	Differences between conditions (df=33) P (lsd)
Tidal volume (litre)					
PA 0.5 kPa	1.033	0.976	0.913	0.974	
PA 1.0 kPa	1.162	1.083	1.000	1.082	≤0.001
SIMVm	0.791	0.881	0.855	0.842	(0.151)
SIMVs	0.722	0.661	0.698	0.693	
Means	0.927	0.900	0.867	0.898	
Diffs between		Ventilators (df=22)		Runs (df=66)	
P (lsd)		0.233 (0.096)		0.005 (0.114)	
Frequency (bpm)					
PA 0.5 kPa	11.70	11.99	13.58	12.42	
PA 1.0 kPa	12.59	12.63	14.46	13.23	≤0.001
SIMVm	13.06	15.08	13.45	13.86	(1.16)
SIMVs	12.76	15.18	12.80	13.58	
Means	12.53	13.72	13.57	13.27	
Diffs between		Ventilators (df=22)		Runs (df=66)	
P (lsd)		0.143 (1.78)		≤0.001 (1.26)	
Inspiratory time (s)					
PA 0.5 kPa	1.84	1.61	1.42	1.63	
PA 1.0 kPa	1.54	1.47	1.20	1.40	≤0.001
SIMVm	1.70	1.01	1.66	1.46	(0.15)
SIMVs	1.93	1.53	2.08	1.85	
Means	1.75	1.41	1.59	1.58	
Diffs between		Ventilators (df=22)		Runs (df=66)	
P (lsd)		0.002 (0.24)		≤0.001 (0.25)	
Contraction phase time (s)					
PA 0.5 kPa	1.60	1.46	1.30	1.45	
PA 1.0 kPa	1.22	1.21	1.09	1.17	≤0.001
SIMVm	1.38	1.03	1.37	1.26	(0.15)
SIMVs	1.58	1.33	1.70	1.54	
Means	1.45	1.26	1.36	1.36	
Diffs between		Ventilators (df=22)		Runs (df=66)	
P (lsd)		0.023 (0.14)		0.026 (0.25)	
Ventilation (litre min^{-1})					
PA 0.5 kPa	11.64	10.93	11.92	11.50	
PA 1.0 kPa	14.00	12.76	13.99	13.58	≤0.001
SIMVm	10.58	12.53	11.51	11.54	(1.43)
SIMVs	9.45	10.83	9.44	9.91	
Means	11.42	11.76	11.71	11.63	
Diffs between		Ventilators (df=22)		Runs (df=66)	
P (lsd)		0.694 (1.22)		≤0.001 (1.16)	
$P_{mus\ peak}$ (kPa)					
PA 0.5 kPa	−0.904	−0.833	−0.704	−0.814	
PA 1.0 kPa	−0.684	−0.686	−0.501	−0.624	≤0.001
SIMVm	−0.792	−0.624	−0.838	−0.751	(0.156)
SIMVs	−0.886	−0.775	−0.992	−0.884	
Means	−0.817	−0.729	−0.759	−0.768	
Diffs between		Ventilators (df=22)		Runs (df=66)	
P (lsd)		0.21 (0.136)		≤0.001 (0.161)	
$P_{mo\ peak}$ (kPa)					
PA 0.5 kPa	0.585	0.611	0.692	0.629	
PA 1.0 kPa	1.085	0.953	1.153	1.064	≤0.001
SIMVm	0.529	1.256	0.535	0.773	(0.076)
SIMVs	0.243	0.301	0.102	0.215	
Means	0.611	0.780	0.620	0.670	
Diffs between		Ventilators (df=22)		Runs (df=66)	
P (lsd)		≤0.001 (0.126)		≤0.001 (0.123)	
PEEP (kPa)					
PA 0.5 kPa	0.054	0.068	0.023	0.048	
PA 1.0 kPa	0.056	0.067	0.025	0.049	0.166
SIMVm	0.056	0.082	0.027	0.055	(0.011)
SIMVs	0.055	0.058	0.024	0.046	
Means	0.055	0.069	0.025	0.050	
Diffs between		Ventilators (df=22)		Runs (df=66)	
P (lsd)		≤0.001 (0.019)		0.11 (0.015)	
P_{mus} (kPa)					
PA 0.5 kPa	−0.177	−0.067	−0.120	−0.121	
PA 1.0 kPa	−0.169	−0.077	−0.122	−0.123	≤0.001
SIMVm	−0.183	−0.075	−0.112	−0.123	(0.011)
SIMVs	−0.163	−0.028	−0.113	−0.101	
Means	−0.173	−0.062	−0.117	−0.117	
Diffs between		Ventilators (df=22)		Runs (df=66)	
P (lsd)		≤0.001 (0.024)		≤0.001 (0.02)	

ever, $P_{mo\ pk}$ was not significantly greater in the PB7200 than in the Veolar or (except at 1.0 kPa PA) in the Elvira. Therefore, it may be that the more rapid initial increase in pressure or the initial oscillation in the PB7200 was in some way responsible. In SIMV it is flow and tidal volume which are controlled by the ventilator. In the Elvira, the short inspiratory time, combined with a tidal volume similar to that of the other ventilators, led to a much larger $P_{mo\ mn}$ and $P_{mo\ pk}$, but the flow waveform was notably different in the Elvira (more of a ramp than a sine wave). There is also the question of why subjects preferred a shorter inspiratory time on the Elvira for CMV (and hence had it imposed on them in SIMV). Again it seems that waveform, this time of flow, may be responsible. Thus there may still be opportunities to improve the acceptability of ventilator assistance by experimenting with the shape of the pressure or flow waveforms.

The low trigger pressures found with the Elvira are probably because it is flow-triggered whereas the versions of the Veolar and PB7200 used were pressure-triggered. (The PB7200 can be flow-triggered in the "flow-by" mode and a new version of the Veolar has flow-triggering as an option.) When discussing trigger sensitivity it is also important to consider the response time of the trigger–a sensitive trigger with a slow response can appear the same to a patient as an insensitive trigger with a rapid response. This is because, in both cases, the inspiratory assistance could occur at approximately the same time after the start of a given p_{mus} waveform, and therefore at the same magnitude of p_{mus}.

In pressure triggering, the ventilator controls the triggering pressure; in flow triggering it does not. This can explain why P_{trig} was more consistent between subjects with the pressure-triggered PB7200 than with the flow-triggered Elvira. However, it does not explain why P_{trig} was more variable with the pressure-triggered Veolar than with the PB7200. However, in pressure assistance, once triggered, the pressure generated by the ventilator increases more rapidly in the PB7200 than in the Veolar. Therefore, the decrease in p_{mo} which occurs at the start of the contraction phase might be reversed immediately the triggering pressure was reached in the PB7200, so that the minimum mouth pressure (which was recorded as P_{trig}) was indeed very close to the triggering pressure of the ventilator. In the Veolar, however, varying rates of increase in p_{mus} (in different subjects) might lead to a variable further decrease in p_{mo}, below the true triggering pressure of the ventilator, before the more gradually increasing generated pressure reversed the effect of the increasing p_{mus}.

The differences in the responses of subjects to different ventilators suggest that, apart from consistent differences between ventilators, different subjects might "prefer" different ventilators. Indeed, although nine subjects voiced a preference for the Veolar at the end of the experimental run, one preferred the Elvira, one the PB7200 and one abstained.

A companion article[18] investigated the factors influencing the reduction in contraction phase time and provides a standard p_{mus} waveform in addition to a method of adapting such a waveform to simulate the response of a normal healthy subject to the conditions investigated here. The next stage is to obtain similar information from patients when they are receiving ventilatory assistance.

Appendix 1

CALCULATION OF P_{mus}

The equation of motion of Mead and Agostoni[19] is:

$$p_{mo}-p_{mus}=R\dot{v}+Ev$$

where p_{mo} and p_{mus}=mouth pressure and respiratory muscle equivalent pressure, R and E=total respiratory resistance and total respiratory elastance, respectively, $\dot{v}$=instantaneous flow, and v=instantaneous volume in the lungs, expressed as a difference from the equilibrium volume.

In the experimental work, $\dot{v}$ is still instantaneous flow, so that the pressure difference across the resistance, R, is:

$$p_{mo}-p_{a}=R\dot{v} \qquad \text{(A1)}$$

where p_a=pressure in the "alveoli" (fig. 1), not true alveolar pressure because R, resistance which separates the "alveoli" from the mouth, is total respiratory resistance. However, after various corrections,[3] the experimentally measured volume is expressed as the difference from the mean end-expired volume instead of the difference from the equilibrium volume. The discrepancy can be resolved as follows.

The definition of elastance, E (total elastance between the "alveoli" and the ambient atmosphere) is the change in pressure difference across the elastance unit, per unit change in volume within the unit:

$$E=\frac{\Delta(p_{a}-p_{mus})}{\Delta v} \qquad \text{(A2)}$$

The pressure difference across E is therefore given by:

$$\Delta(p_{a}-p_{mus})=E\,\Delta v \qquad \text{(A3)}$$

At the mean end-expired volume let

$$p_{a}=P_{aEF}$$

and

$$p_{mus}=P_{musEF}$$

Then equation (A3) becomes:

$$(p_{a}-P_{aEF})-(p_{mus}-P_{musEF})=Ev \qquad \text{(A4)}$$

where v is now experimentally measured volume.

Eliminating p_a from equations (A4) and (A1) gives:

$$p_{mus}=p_{mo}-R\dot{v}-Ev+(P_{musEF}-P_{aEF}) \qquad \text{(A5)}$$

If the subjects completely relax their respiratory muscles during CMV for determination of elastance and resistance, then p_{mus} and P_{musEF} are both zero. Also, at end-expiration, $p_{mo}=P_{moEF}=P_{aEF}+R\dot{v}_{E}$ (from equation (A1)). Therefore, rearranging equation (A5),

$$p_{mo}-P_{moEF}=R(\dot{v}-\dot{v}_{E})+Ev \qquad \text{(A6)}$$

P_{moEF} can be obtained from the pressure recording. Therefore, with measurement of p_{mo}, $\dot{v}$ and v, elastance and resistance can be estimated by a multiple regression technique.

For the main, spontaneous breathing runs, equation (A5) can be rearranged to:

$$p_{mus}=p_{mo}-(P_{moEF}-R\dot{v}_{E})-R\dot{v}-Ev+P_{musEF} \qquad \text{(A7)}$$

Thus with elastance and resistance known, and p_{mo}, $\dot{v}$ and v measured continuously, p_{mus} can be calculated, apart from the unknown constant P_{musEF}. Therefore, the shape of the p_{mus} waveform can be determined but there is uncertainty about its zero position.

Appendix 2

AVERAGING OF P_{mus} WAVEFORMS

Simply averaging all p_{mus} waveforms in an overlay graph could distort the waveform. For instance, if the duration of the contraction phase varies from breath to breath in a run, this would result in an "average" waveform with a blunt peak that is not typical of any of the breaths in the run.

Examination of the overlay plots from all the runs in the study showed that the waveforms in the contraction phases of successive breaths generally set off on the same trajectory, but "dropped off" at different times. It was the duration to, and magnitude of, the peak, rather than the shape of the contraction phase which varied from breath to breath during a run. Therefore each p_{mus} waveform was divided, at its (negative) peak, into the contraction and relaxation phases which were averaged separately. This preserved the trajectories of the two phases.[3]

To obtain the mean waveform of the contraction phase for a run, a segment of the waveform, from 1 s before the start of inspiratory flow to the time of $P_{mus\ pk}$, was extracted for each breath

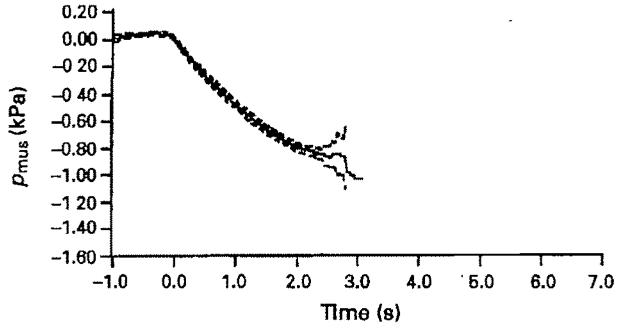

Figure A1 Mean waveform and 95% confidence limits of the contraction phase of p_{mus} for the breaths of a sample run. This waveform was subsequently truncated to the mean contraction phase time for the run–2.46 s.

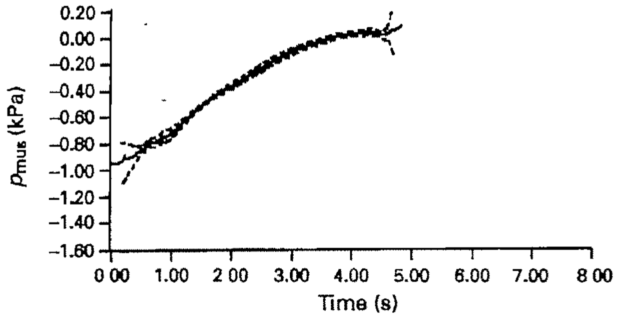

Figure A2 Mean waveform and 95% confidence limits for the synchronized relaxation phases of the breaths shown in figure A1.

and stored in successive rows of a two-dimensional matrix. For each column of the matrix (representing successive times) the mean and SD of the values in the occupied rows were calculated to yield the mean contraction phase waveform for the run and its 95% confidence limits (fig. A1) shows the mean and confidence limits of the contraction phases of the breaths in a sample run. The "flare" of the confidence limits at the end of the mean waveform is caused by tailing off of the number of breaths included in the average, ultimately ending with a single breath (when confidence intervals cannot be calculated). The mean waveform and confidence limits were always truncated to the mean time of the end of the contraction phase, this avoided the extreme flares that sometimes occurred at the end of the contraction phase.

The relaxation phases were first time-shifted in relation to one another for optimum synchronization. To remove the influence of noise and irregularity in the waveform, a second order polynomial (previously found to give a good fit to relaxation phases) was first fitted to the relaxation phase of each breath. The times at which these fitted curves (one for each relaxation phase in a recording) crossed 0.75 of the smallest $P_{mus\,pk}$ for that recording were synchronized. This procedure produced a close overlay of the individual raw relaxation phases, as indicated by the relatively constant width of the confidence limits except at the extreme ends of the waveform (fig. A2). As a result of the synchronization procedure, there was flaring of the confidence limits at both ends of the waveform as relaxation phases "dropped in" at the start and "dropped out" at the end (fig. A2). Examination of many of the overlay graphs showed that this procedure preserved the shape of the relaxation phase.

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Ventilatory assistance and respiratory muscle activity. 2: Simulation with an adaptive active ("aa" or "a-squared") model lung

J. S. MECKLENBURGH AND W. W. MAPLESON

Summary

The aim of this study was to develop a lung model which adapted its active simulation of spontaneous breathing to the ventilatory assistance it received–an "aa" or "a-squared" lung model. The active element required was the waveform of negative pressure (p_{mus}), which is equivalent to respiratory muscle activity. This had been determined previously in 12 healthy volunteers and comprised a contraction phase, relaxation phase and expiratory pause. Ventilatory assistance had shortened the contraction and relaxation phases without changing their shape, and lengthened the pause phase to compensate. In this study, the contraction and relaxation phases could be adequately represented by two quadratic equations, in addition to a third to provide a smooth transition. Therefore, the adaptive element required was the prediction of the duration of the contraction phase. The best predictive variables were flow at the end of contraction or peak mouth pressure. Determination of either of these allowed adjustment of the "standard" waveform to the level of assistance produced by an "average" ventilator, in a manner that matched the mean response of 12 healthy conscious subjects. (*Br. J. Anaesth.* 1998; **80**: 434–439)

Keywords: model, lung; ventilation, spontaneous; ventilation, artificial; muscle respiratory; equipment, ventilators

Spontaneous breathing has been simulated by various techniques in order to test ventilators.[1–4] Most of these techniques do not allow realistic interaction between the assistance generated by the ventilator and the activity of the respiratory muscles of the patient. In a previous article[5] a model was described that interacted realistically: it reproduced the waveforms of flow and pressure at the mouth generated by a subject breathing through a ventilator set to each of a range of modes of operation. The model required a knowledge of the subject's compliance, resistance and respiratory muscle activity, as represented by the equivalent waveform of (negative) generated pressure, p_{mus}. This is defined[5] as that pressure which, if the subject's respiratory muscles were paralysed, and the waveform of p_{mus} were applied to the outside of the subject's thorax, the waveforms of flow and pressure at the mouth of the subject would be the same as before paralysis.

To provide a model lung with the equivalent of spontaneous respiratory muscle activity, a mathematical representation of the typical waveform of p_{mus} is required. In addition, a mechanism is needed to change that representation in the way that the waveform of p_{mus} changes in response to the assistance or load imposed by any ventilator or breathing system under investigation.

A companion article[6] described the interaction between spontaneous respiratory muscle activity and ventilatory assistance or a resistance load in healthy volunteers. The main findings of that article were: (1) p_{mus} increased progressively during the contraction phase of the muscles and (2) on average, the trajectory of this increase remained constant, but the duration of the phase increased with resistance loading and decreased with ventilatory assistance. Consequently there were corresponding changes in the amplitude of p_{mus} with the various conditions. There were similar changes in the duration of the relaxation phase: it increased with resistance loading and decreased with ventilatory assistance. Despite the shortening of the contraction and relaxation phases with ventilatory assistance, the frequency, and hence respiratory period, was the same for all types of assistance when averaged over all three ventilators. Thus the reduction in contraction and relaxation phase times was coupled with an extension of the expiratory pause. With a resistive load, the contraction phase time increased by 10% and the respiratory period increased by 8%.

This article describes the formation of a mathematical representation of spontaneous respiratory muscle activity and also provides a relationship between imposed assistance or load and duration of the phases of the p_{mus} waveform. This information provides the basis for an "adaptive active" ("aa" or "a-squared") model lung which can respond automatically to loads and assistance in the same way as healthy volunteers.

Thus this article uses data from healthy volunteers to establish the technique. Subsequent extension of the work to provide similar data from patients in need of ventilatory support should permit the application of the technique to those data and so lead to clinically relevant findings.

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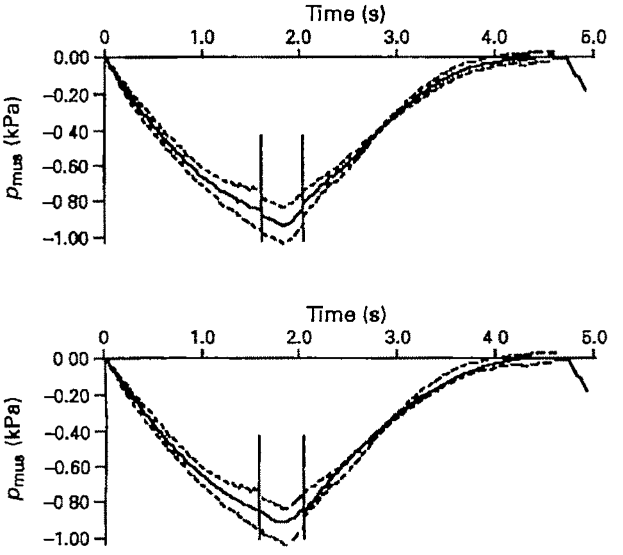

Figure 1 Top: complete overall mean waveform for the unloaded, unassisted condition, constructed from the all-subject means for each phase: contraction, peak and relaxation. The boundaries between the phases are marked by vertical lines. A short length of zeros pads the waveform to the mean duration for this condition, and a short length of the contraction phase is repeated. The broken lines indicate the 95% confidence limits for the position of the waveform for each phase. Bottom: the curves of parabolas fitted to each of the three phases, together with the 95% confidence limits of the mean waveform from the top graph.

Subjects and methods

DATA COLLECTION AND PROCESSING

Waveforms of p_{mus} were obtained from 12 healthy volunteers breathing under five different conditions[6]: unloaded; resistance loaded, 0.5 kPa s litre^{-1} (at 1 litre s^{-1}); pressure assistance of 0.5 kPa; pressure assistance of 1.0 kPa; and synchronized intermittent mandatory ventilation (SIMV) at a frequency of 6 bpm (breaths coincident with mandatory inflations were processed separately from the spontaneous-only breaths).

The ventilators used were the Hamilton Veolar, Engström Elvira and Puritan Bennett 7200.

Details of the experimental procedure, data collection and processing are given in the accompanying article.[6]

PROCESSING OF EXPERIMENTAL DATA

The data forming the basis of the simulation were in the form of a mean p_{mus} waveform for the unloaded condition, together with numerical data describing the effect on this waveform of resistance loading and ventilator assistance.

The averaging procedures used in the companion article[6] to produce mean contraction phase and mean relaxation phase waveforms produced a slightly distorted shape at the end of the contraction phase and start of the relaxation phase. In order to obtain a smooth transition from the contraction to the relaxation phase a peak phase was defined, comprising the last 0.24 s of the contraction phase and first 0.24 s of the relaxation phase. The waveforms of these three (overlapping) phases were averaged over all breaths in each condition for each subject and then averaged over the 12 subjects. The resulting means for the three phases in the unloaded, unassisted condition are shown in figure 1 (top) together with 95% confidence limits. The transitions between the three phases, indicated by vertical lines, were chosen as the times, within ±0.24 s of the peak, where the relevant waveforms were most nearly coincident. The discontinuities at the joins arise because of the different durations of the contraction and relaxation phases in different subjects.[6]

MATHEMATICAL FITTING PROCEDURES

To reduce this waveform to a set of equations, a separate polynomial equation was first fitted to the mean data for each phase by a least-squares fitting procedure (General LS Polynomial Fit, LabView ver. 3.1, National Instruments). Adjustments were then made to the fitted curves (see below) to achieve smooth transitions between adjacent phases.

ADAPTATION OF FITTED WAVEFORM

It was noted in the accompanying article[6] that almost the only effect of ventilatory assistance and resistance loading on the all-subject mean waveform was a change in durations of the contraction and relaxation phases. Therefore, to make an "a-squared" (adaptive active) model lung which could mimic the response of the average volunteer to the various forms of assistance and loading, it is necessary to predict the appropriate contraction time, T_c (from the start of contraction to the peak of contraction) from variables which can be measured.

The companion article[6] distinguishes two possible types of control of the contraction time during ventilatory support: breath-to-breath, in which the contraction time in any breath depends on what happened in previous breaths, and within-breath, in which the contraction time is determined by what is happening in the current breath. Explanatory variables, derived from the continuous measurement of flow ($\dot{v}$), volume (v) and pressure at the mouth (p_{mo}),

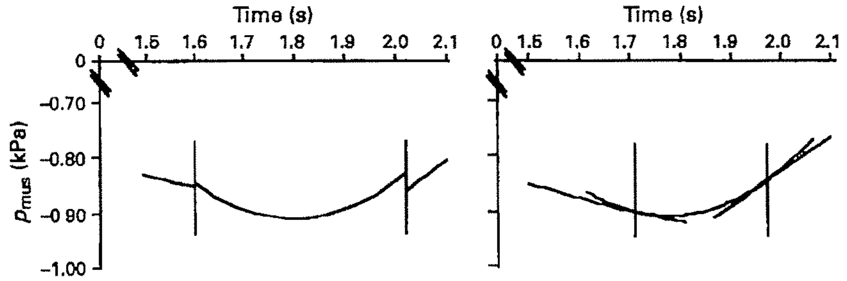

Figure 2 Expanded centre section of figure 1 (bottom) showing the discontinuities between the unadjusted parabolas (left) compared with the tangency of the adjusted ones (right) and the smooth transitions between them.

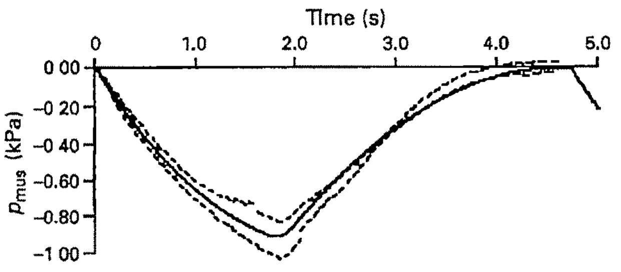

Figure 3 Adjusted parabolas, as in figure 2, but each truncated to the point(s) of tangency. The 95% confidence limits (broken lines) of the experimental mean waveforms are overlaid.

fall into two corresponding groups. First, there are those variables that can be derived only from the whole inspiratory phase, for example peak mouth pressure ($P_{mo\ peak}$) and mean flow ($\dot{v}_{mean}$). These variables can be used only in a breath-to-breath control mechanism. Second, there are variables derived from values at the peak of contraction (i.e. at T_c) for example mouth pressure at T_c ($P_{mo\ atTc}$). These could form the basis of a within-breath control mechanism. Multiple regression (Minitab ver. 8.2 running on various models of Apple Macintosh using system 7.1 or 7.5) was used to examine the dependence of T_c on the all-subject means[6] of the measured variables in these two groups.

Results

MATHEMATICAL FITTING OF THE MEAN, UNLOADED P_{MUS} WAVEFORM

Second-order polynomials (parabolas) were considered to give an adequate fit to each of the three phases: those for the contraction phase and the peak lay close to the middle of the experimental confidence limits (fig. 1, bottom); the parabola for the relaxation phase swung from one confidence limit to the other and back again and marginally breached the upper limit near where the limits are narrowest. (Reasons for accepting this as adequate are given in the discussion.) However, the abutment between the parabolas showed unrepresentative discontinuities in the fitted waveform (fig. 2, left).

These discontinuities were eliminated as follows. A new parabola, constrained to pass through the origin, was fitted to the contraction phase (the unconstrained parabola produced a small, non-significant intercept, 0.0024 kPa). In the resulting parabola, the curvature (the square coefficient c in $p=a+bt+ct^2$) was then adjusted (from 0.1886 to 0.1848) to make the contraction parabola tangent to the fitted peak parabola, with the intercept a and initial slope b unaltered. In the fitted relaxation parabola, the shape was maintained but the position of the parabola was shifted, first in the pressure direction (by −0.020 kPa) to move the apex from its free, slightly positive position to zero, and then in the time direction (by −0.036 s) to make it tangent to the peak parabola. Figure 2 (right) shows the points of tangency in detail. The relaxation parabola was terminated at the apex (at zero pressure) and the remainder of the mean respiratory period was represented by a flat line at zero p_{mus}.

The complete, adjusted waveform, with transitions from each parabola to the next at the points of tangency, forms a smooth curve (fig. 3), falling well within the experimental confidence limits, apart from the minor discrepancies already noted in the relaxation phase.

The coefficients for the adjusted waveform are: for t=0 to 1.71 s (main part of the contraction phase),

$$p_{mus}=0.0–0.8445\,t+0.1848\,t^2; \qquad (1)$$

for t=1.71–1.97 s (peak phase),

$$p_{mus}=4.4408–6.0281\,t+1.6975\,t^2; \qquad (2)$$

for t=1.97–4.59 s (relaxation phase–main part),

$$p_{mus}=-2.5980+1.1317\,t-0.1232\,t^2; \qquad (3)$$

and for t=4.59–4.74 s (terminal part of the waveform),

$$p_{mus}=0 \qquad (4)$$

Table 1 Regression results for the prediction of contraction time, T_c, from characteristics of the complete inspiratory phase; b_0=intercept, b_1, b_2,=slope coefficients for the first and second explanatory variables; SE=standard error of the coefficient; RSD=residual standard deviation of the regression; P=probability that the improvement of fit produced by the only, or by the second, explanatory variable is caused by chance. T_c is in seconds, pressures are in kPa, flows in litre s^{-1}, and volume in litres

	Regression coefficients				
Explanatory variables	b_0 (SE)	b_1 (SE)	b_2 (SE)	RSD	P
$P_{mo\ pk}$	1.833 (0.050)	−0.666 (0.075)		0.134	<0.0001
$\dot{v}_{mn}$	2.358 (0.111)	−1.587 (0.196)		0.145	<0.0001
$P_{mo\ mn}$	1.768 (0.059)	−0.909 (0.141)		0.173	<0.0001
$\dot{v}_{pk}$	2 304 (0.137)	−0.985 (0.161)		0.180	<0.0001
V_T	2.483 (0.423)	−1.135 (0.486)		0.293	0.035
$P_{mo\ pk}+V_T$	1.047 (0.166)	−0.951 (0.075)	1.079 (0.223)	0.083	0.0003
$\dot{v}_{mn}+V_T$	1.806 (0.163)	−2.280 (0.227)	1.075 (0.278)	0.103	0.002
$P_{mo\ mn}+V_T$	0.369 (0.212)	−1.717 (0.140)	1.900 (0.286)	0.086	<0.0001
$\dot{v}_{pk}+V_T$	1.896 (0.265)	−1.319 (0.242)	0.790 (0.450)	0.168	0.10

Table 2 Regression results for the prediction of contraction time, T_c, from characteristics at the end of the contraction phase of p_{mus}. Nomenclature as in table 1

	Regression coefficients				
Explanatory variables	b_0 (SE)	b_1 (SE)	b_2 (SE)	RSD	P
$\dot{v}_{atTc}$	2.446 (0.099)	−1.796 (0.181)		0.122	<0.0001
$P_{mo\ atTc}$	1.793 (0.063)	−0.965 (0.153)		0.176	<0.0001
$\dot{v}_{atTc}+V_{atTc}$	1.922 (0.187)	−1.908 (0.148)	0.844 (0.273)	0.096	0.009
$P_{mo\ atTc}+V_{atTc}$	0.504 (0.112)	−1.280 (0.054)	2.001 (0.171)	0.054	<0.0001

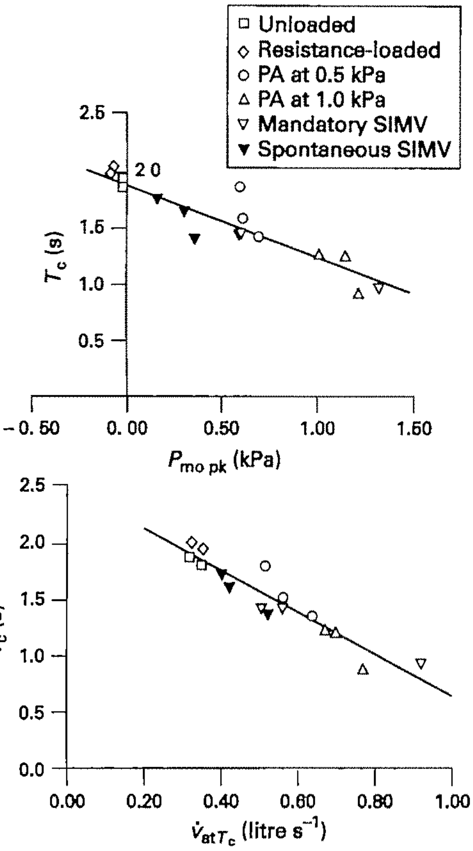

Figure 4 Contraction time (T_c) plotted against peak mouth pressure ($P_{mo\,pk}$) and flow at Tc ($\dot{v}_{atTc}$) under the conditions: unloaded, resistance-loaded, pressure assistance (PA) at 0.5 kPa, PA at 1.0 kPa, mandatory and spontaneous breaths in SIMV. For the unloaded and resistance-loaded conditions there are two symbols representing "before" and "after" the sequence of ventilator runs; for PA and SIMV there are three symbols representing the three ventilators.

where t=time (in s) from the start of the p_{mus} waveform and p_{mus} is in kPa.

RELATIONSHIP BETWEEN CONTRACTION TIME, T_c, AND CHARACTERISTICS OF RESISTANCE LOADING OR VENTILATOR ASSISTANCE

For the breath-by-breath mechanism of control, contraction time (T_c) showed a significant dependence on all five of the possible predictors, but barely so for tidal volume, *V*T (table 1). For the within-breath mechanism of control, T_c showed a dependence on flow at T_c, ($\dot{v}_{atTc}$) and mouth pressure at T_c ($P_{mo\,atTc}$) (table 2) but not for volume at T_c. When *V*T was added as a second predictor to each of the other variables in table 1, or when volume at T_c (V_{atTc}) was added to each variable in table 2, there was a significant improvement in fit (reduced residual SD) but in both cases the coefficient of the added variable was positive. This indicates that T_c increases with *V*T or V_{atTc}, whereas the classical theory of termination of inspiratory effort is that increase in tidal volume leads to a decrease in T_c. Therefore, it must be concluded that the positive coefficient is a manifestation of the dependence, not of T_c on volume, but of volume on T_c–the longer the subject continues to increase p_{mus}, the greater the tidal volume inspired. Accordingly, volume cannot be used in the control of T_c. Therefore, given the present data, the prediction of T_c must be based on a single variable.

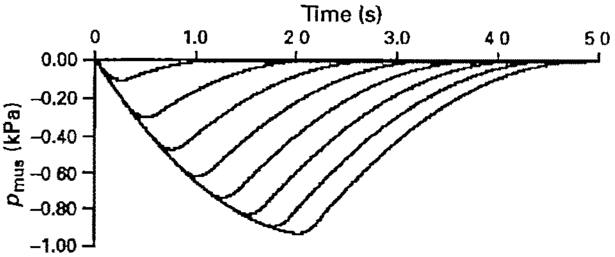

Figure 5 Illustration of algebraically specified p_{mus} waveforms with different contraction times corresponding to different degrees of ventilatory assistance and, at T_c=2 s, a small degree of resistive loading, and then ensuring smooth transitions between parabolas by the method of Mecklenburgh.[7] Waveforms are included for contraction times of 0.25–2.0 s in 0.25-s steps. Note that the minimum mean contraction time observed was 1.0 s but the curves shown for shorter times are reasonably representative of those found in some subjects.

The best predictive equations are:

$$T_c=2.446-1.796\,\dot{v}_{atTc} \qquad (5)$$

$$T_c=1.833-0.666\,P_{mo\,pk} \qquad (6)$$

with residual SD values of 0.122 s and 0.134 s, respectively; therefore flow at the end of the contraction phase, $\dot{v}_{atTc}$, is a marginally better predictor than peak mouth pressure, $P_{mo\,pk}$.

These equations are plotted in figure 4, together with the data points to which they were fitted, using different symbols for each condition. Surprisingly these equations apply equally to the volume-controlled modes (where tidal volume and inspiratory time are set on the ventilator) as to the pressure-assistance modes. This can be claimed because the mandatory breaths in SIMV lie within the spread of the other points in figure 4.

Discussion

FIT OF PARABOLAS TO EXPERIMENTAL DATA

The three parabolas provided a smooth curve which closely followed the mean observed waveform of p_{mus} for the unloaded condition, except for a somewhat different shape during relaxation (fig. 3); this led to a marginal breach of the upper confidence limits where the limits are narrow. Adding a third term, dt^3, to the equation for the relaxation phase improved the fit over the central part of relaxation, but weakened it at the end. There are grounds for ignoring this breach of confidence limits: narrowing of the limits in the middle of the relaxation phase is artificial; it arises from deliberately synchronizing the different component waveforms at this point.[7] Other fitting methods were considered but any that improved the fit appreciably did so at the expense of increasing the complexity of the equation for the complete waveform. This increase in complexity would be a major drawback for implementing an active model lung.

Thus equations (1)–(4) provide an adequate mathematical representation of the waveform of p_{mus} for healthy volunteers, during quiet breathing under normal, unloaded, unassisted conditions. They could therefore be used to quantify an active lung model such as that of Mecklenburgh, Al-Obaidi and Mapleson.[5]

Similar equations are given for the same purpose in BS 5724:3:12[8] "Method of declaring the performance parameters of lung ventilators". The individual coefficients differ considerably from those given here, but the resulting waveform is very similar.[7] The equations in BS 5724:3:12 were obtained in this department in a similar manner to that described here, but were based on only three subjects. Therefore, the present equations, based on 12 subjects, should provide a better representation for the healthy volunteer.

USING THE PREDICTION EQUATION IN AN "A-SQUARED" MODEL

For an active lung model to be truly versatile it must be capable of adjustment to provide varying magnitudes of respiratory muscle effort and various frequencies of breathing. BS 5724:3:12 specifies that this adjustment should be done "manually" by scaling the waveform appropriately in amplitude and duration and by extending the duration of zero p_{mus} at the end of the relaxation phase for respiratory frequencies less than 6 bpm. However, our study provides quantitative information on the way that the average healthy subject responds to resistance loading and ventilatory assistance. Therefore, a model in which the p_{mus} waveform was basically defined by equations (1)–(4), but in which T_c was governed by equation (5) or (6), would constitute an "a-squared" model which would respond to pressure assistance and SIMV (and resistance loading–see below) in the same way as the mean of the 12 subjects used here. However, adapting equations (1)–(4) to changes in T_c involves several steps.

ADAPTATION OF MEAN FITTED WAVEFORM TO LOADING AND ASSISTANCE

The total respiratory period in normal, unloaded breathing was 4.7 s. Ventilatory assistance decreased the period by up to 9% (ns); resistance loading increased it by 8%, to 5.1 s.[6] For ventilator testing it would be convenient and reasonable to set the period to 5 s for all levels of assistance and resistance *within the range of T_c encountered* (approximately 1–2 s). This would give an integer value for frequency of 12 bpm.

When the contraction and relaxation phases shorten, the beginning of the former and the end of the latter remain the same; it is the portions around the peak that are omitted.[6] Therefore, to adapt the basic waveform to various types and magnitudes of resistance loading and ventilatory assistance, it is necessary to decrease the contraction phase time, decrease the relaxation phase time, and then increase the expiratory pause to make up the constant 5-s respiratory period. The procedure used to achieve this with the appropriate smooth transitions from contraction to peak and from peak to relaxation was as follows.

The peak parabola was time-shifted so that its peak occurred at the required T_c, and pressure-shifted so that it was tangent to the contraction phase parabola. Then the relaxation phase parabola was time-shifted to make it tangent to the shifted peak parabola. The remainder of the respiratory period was then padded with zeros.

A method for producing tangent parabolas[7] has been used to generate the range of p_{mus} waveforms shown in figure 5 which represent adaptation to several levels of assistance and, at T_c=2 s, a small degree of resistive loading.

This adaptation of the p_{mus} waveform could be performed on-line during the laboratory testing of ventilators. Measurement of $\dot{v}_{atTc}$ or $P_{mo\,pk}$ poses few problems and, when a value had been obtained for a few breaths, the contraction phase time could be adjusted, with iteration of measurement and adjustment until the relationship between T_c and $\dot{v}_{atTc}$ or $P_{mo\,pk}$ accorded sufficiently closely with equation (5) or (6).

With equation (6) there seems no danger of the iteration "running away" because reducing T_c in response to $P_{mo\,pk}$ would mean that, in pressure assistance, there would be less time for the ventilator to generate the set pressure which would result in the same or lower $P_{mo\,pk}$, leading to less reduction in T_c than initially calculated–negative feedback. In triggered CMV with time-cycled flow generation in the inspiratory phase, the mandatory breath would continue irrespective of the shortening of T_c. As a result, with a decreased T_c, $P_{mo\,pk}$ would increase at the end of the inflation because the decreased p_{mus} would increase the "alveolar" pressure. This would lead to a further reduction in T_c, but a much smaller one than the initial reduction based on the first inflation, because of the much smaller increase in $P_{mo\,pk}$. Therefore, although there is positive feedback, it would rapidly diminish. In any case a limit is reached if contraction phase time reduces to zero when $P_{mo\,pk}$ would be determined only by the passive properties of the model. It is unclear how to make the "a-squared" model lung adapt independently to the mandatory and spontaneous breaths in SIMV; some algorithm would be needed to permit identification of the type of breath (mandatory or spontaneous) to allow separate processing.

Although equation (5) was devised for use for within-breath control of T_c, figure 5 shows that the point of transition from contraction to peak parabola varies with T_c. This would make implementation of within-breath control mathematically complex. However, with iteration it would be possible to "home in" on the appropriate T_c.

Thus we have developed a mathematical representation of the activity of the respiratory muscles of healthy volunteers. We have also shown how this representation can be modified in response to resistance loading and ventilator assistance in a manner that mimics the mean response of our healthy volunteers. We plan to extend this work to patients requiring ventilatory assistance so that an active lung model can be made to respond in a manner typical of patients, or at least of patients in specific circumstances, for example in anaesthesia, intensive care or recovering from cardiovascular surgery.

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Effect of different doses of inhaled nitric oxide on pulmonary capillary pressure and on longitudinal distribution of pulmonary vascular resistance in ARDS

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Summary

Inhaled nitric oxide lowers pulmonary capillary pressure (PCP) in animals and in patients with acute respiratory distress syndrome (ARDS). A dose–response relationship in patients with ARDS has not yet been established. Therefore, we studied the effects of four concentrations of nitric oxide (1, 10, 20 and 40 volumes per million (vpm)) in random order, on PCP in 19 patients with ARDS. PCP was estimated by visual analysis of the pressure decay curve after balloon inflation of the pulmonary artery catheter. Haemodynamic and gas exchange variables were measured at each nitric oxide concentration. Patients were classified as responders when PCP decreased by at least 2 mm Hg after nitric oxide 20 vpm. In responders (n=8), nitric oxide decreased PCP and post-capillary vascular resistance dose-dependently and changed longitudinal distribution of pulmonary vascular resistance with a maximum effect at 20 vpm. In non-responders (n=11), PCP did not change. In both groups, the nitric oxide-induced decrease in pre-capillary vascular resistance was small with a maximum effect at 1 vpm. In ARDS, vasodilatation of pre-capillary vessels is achieved at low concentrations of nitric oxide, whereas the effect of nitric oxide on post-capillary vessels is variable. Higher concentrations may be required for optimal post-capillary vasodilatation in a subgroup of ARDS patients. (*Br. J. Anaesth.* 1998; **80**: 440–446)

Keywords: lung, acute respiratory distress syndrome; pharmacology, nitric oxide; lung, vasculature

Arterial hypoxaemia and bilateral infiltrates on the chest radiograph in the absence of left atrial hypertension are features of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).[1] Arterial hypoxaemia, defined as the ratio of arterial oxygen tension (Pa_{O_2}) to inspired fraction of oxygen (FI_{O_2}) is more severe in ARDS (Pa_{O_2}/FI_{O_2} <26.7 kPa) compared with ALI (Pa_{O_2}/FI_{O_2} <40 kPa).[1] In the early stages of ALI and ARDS, these features are the result of enhanced microvascular permeability and increased transvascular fluid filtration with non-cardiogenic oedema.

Transvascular fluid filtration depends on the filtration coefficient, reflection coefficient and on hydrostatic and oncotic pressure differences.[2] In the presence of a capillary leak, as occurs in ALI and ARDS, the reflection coefficient approaches zero and intracapillary hydrostatic pressure becomes the decisive force in governing transvascular fluid filtration, that is oedema formation. In ALI and ARDS, constriction of post-capillary vessels may result in increased pulmonary capillary pressure (PCP)[3–9] with enhancement of oedema formation. Thus one of the therapeutic goals in the treatment of ALI and ARDS is reduction of PCP.

Inhaled nitric oxide, a selective pulmonary vasodilator,[10–12] has been shown to decrease PCP in animal models of pulmonary hypertension[13 14] and in patients with ALI.[15] Inhaled nitric oxide decreases transvascular fluid filtration in rabbit lungs with oxidant-induced lung injury,[16] in isolated rat lungs with neutrophil-mediated capillary leak[17] and in hydrogen peroxide-challenged rabbit lungs.[18] In patients with ALI, nitric oxide 40 volumes per million (vpm) reduced PCP and transvascular albumin flux.[15 19]

Recently, nitric oxide has been shown to decrease pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) at concentrations lower than 40 vpm.[20–22] The effect of lower nitric oxide concentrations on PCP, however, has not been studied in patients with ALI or ARDS. Therefore, we have investigated the effect of different nitric oxide concentrations on PCP and on longitudinal distribution of PVR in 19 patients with ARDS.

Patients and methods

After obtaining approval from the local Ethics Committee and written consent from the patient's family, we studied 19 consecutive patients with no history of previous lung disease who fulfilled the criteria of ARDS.[1]

The clinical characteristics of the patients are summarized in table 1. The severity of acute lung disease was graded by Murray's lung injury score.[23] The severity of critical illness and additional organ failures were classified by the acute physiology and chronic health evaluation II (APACHE II) score[24] and an organ system failure score.[25] According to this score,

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Table 1 Patients characteristics. *Patients were treated by veno-venous extracorporeal lung assist at time of study. The range of lung injury score is 0–4. A score of 0 indicates no lung injury, a score of 0.1–2.5, mild-to-moderate lung injury and a score of 2.5–4, severe lung injury. Additional organ failures were: liver dysfunction (i.e. bilirubin concentration >34 μmol litre^{-1}, and/or serum transaminase concentrations three times normal), renal dysfunction (i.e. creatinine concentration > 177 μmol litre^{-1}), CNS dysfunction (i.e. coma), coagulation disorders (with or without bleeding), and cardiovascular failure (i.e. haemodynamic support by catecholamines) Patients were classified as responders, when PCP decreased by at least 2 mm Hg at inhaled NO 20 vpm

Pat. No.	Age	Sex	Underlying disease	Days of mechanical ventilation at time of study	Lung injury score[23]	APACHE II score[24]	Additional organ failures[25]	Responder	Survival
1	35	F	Multiple trauma	5	1.75	14	3	Yes	No
2	29	M	Multiple trauma	32	3.25	24	4	Yes	No
3	44	F	Peritonitis	4	3	17	2	No	Yes
4	23	M	Multiple trauma	14	3.5	18	1	Yes	No
5	55	F	Pneumonia, peritonitis	18	3.25	16	1	No	Yes
6	21	F	Fournier's gangrene	7	3	19	0	No	Yes
7*	41	F	Pneumonia	28	3.25	19	2	Yes	Yes
8	47	M	Pancreatitis	10	3.25	15	2	Yes	No
9	24	F	Multiple trauma	3	2.25	11	3	No	Yes
10	49	M	Aspiration pneumonia	5	2.5	23	4	No	Yes
11	55	F	Multiple trauma	21	3.5	18	2	Yes	Yes
12*	14	M	Peritonitis	34	3.5	17	1	Yes	Yes
13	44	M	Pneumonia	16	3.25	22	2	Yes	No
14	53	M	Multiple trauma	4	2.5	12	3	No	No
15	34	F	Pneumonia	2	3.5	15	3	No	Yes
16	33	M	Multiple trauma	2	3.25	14	1	No	Yes
17	53	M	Pneumonia	9	3.25	21	1	No	Yes
18	46	M	Near-drowning	14	3.25	21	0	No	No
19	63	M	Multiple trauma	4	3.25	21	3	No	No

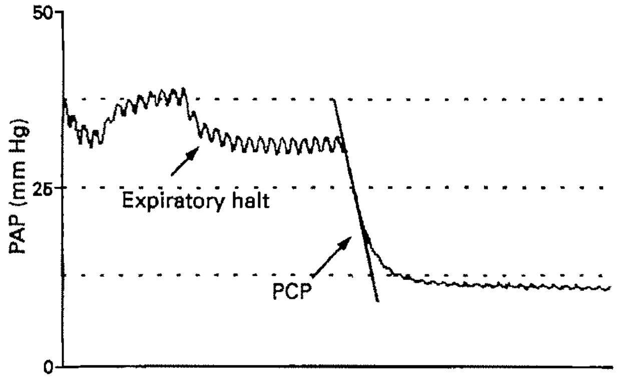

Figure 1 Registration of pressure decay after inflation of the pulmonary artery catheter balloon. Pulmonary capillary pressure (PCP) was estimated as the inflexion point of the pressure decay curve.

dysfunctions of five organ systems were identified: liver dysfunction (i.e. serum bilirubin concentration >34 μmol litre^{-1} or serum transaminase concentrations three times normal, or both), renal dysfunction (i.e. serum creatinine concentration >177 μmol litre^{-1}), coagulation disorders (with or without actual bleeding), host defence failure (i.e. sepsis diagnosed by positive blood cultures) and cardiovascular failure (i.e. catecholamines were required to support systemic circulation). Leucocyte count in peripheral blood and the results of bacteriological examination of tracheal aspirates from the day of study or 1 day before, were recorded as markers of infection.

Patients' lungs were ventilated using a pressure-controlled setting (Servo ventilator 900 C, Siemens Elema, Lund, Sweden) with tidal volumes of 4.9–12.8 ml/kg body weight, ventilatory frequencies of 9–25 bpm and PEEP 8–16 cm H_2O. The fraction of inspired oxygen (FI_{O_2}) was 0.4–1.0. Ventilator settings were not changed throughout the study. Two patients (Nos 7 and 12) were studied during veno-venous extracorporeal lung assist (ECLA). Extracorporeal blood flow was not changed during the study. Patients were sedated with flunitrazepam 2 mg h^{-1} and paralysed with pancuronium 6 mg h^{-1}.

In all patients, a pulmonary artery thermodilution catheter (model SP 1507, Spectramed, Düsseldorf, Germany or Opticath P7110-EP8, Abbott, Wiesbaden, Germany) and a radial arterial catheter were inserted. Systolic, diastolic and mean pulmonary artery pressure (PAP), central venous pressure (CVP), systolic, diastolic and mean arterial pressure (MAP), and heart rate (HR) were monitored continuously. Cardiac output (CO) was determined as the mean of three thermodilution measurements performed randomly during the respiratory cycle using saline 10 ml at room temperature and a cardiac output computer (Sirecust 1281, Siemens, Erlangen, Germany). All pressure measurements were performed at end-expiration with the patient supine and the calibrated pressure transducers (Medex Novotrans II MX 860, Hilliard, OH, USA) zeroed to atmospheric pressure at the midaxillary level. In all patients pulmonary artery wedge pressure (PAWP) was higher than PEEP, suggesting a zone III position of the tip of the pulmonary artery catheter. PCP was estimated by visual analysis of the pressure decay curve after pulmonary artery occlusion, as described by Cope and colleagues.[26] Pulse pressure was reduced by a small container with 0.4 ml of air attached to the side port of the pulmonary artery catheter. When PAP was stable, the balloon of the pulmonary artery catheter was inflated and the pressure profile recorded on a printer (Sirenet, Siemens, Erlangen, Germany) at a chart speed of 6.25 mm s^{-1} until wedge pressure was obtained. The inflexion point, that is PCP, was determined visually by placing a ruler on the rapid component of the pressure decline adjusted for the best fit and marking the point at which the slow component of the pressure profile deviated from the rapid component (fig. 1). Pressure tracings were recorded at end-expiration using the "expiratory halt" function of the

Servo 900 C ventilator for 5–8 s to suppress respiratory artefacts. Three pressure profiles were obtained with each set of measurements. Pressure tracings were analysed separately by two independent investigators (H. K. and A. B.) and the means of the measurements were used for further calculations. The coefficient of variation of the PCP estimation was <4%. After determination of PAP, PCP and PAWP, PVR was calculated using standard formulae and divided into pre-capillary and post-capillary resistance. Pulmonary pre-capillary resistance (PVR_{art}) was calculated as the pulmonary pre-capillary pressure gradient (PAP–PCP) times 80 divided by CO, and pulmonary post-capillary resistance (PVR_{ven}) as the pulmonary post-capillary pressure gradient (PCP–PAWP) times 80 divided by CO. Arterial and mixed venous blood-gas tensions, haemoglobin oxygen saturation, total haemoglobin concentration and packed cell volume were determined using an ABL 510 (Radiometer, Copenhagen, Denmark).

Nitric oxide was administered as described previously.[15] Briefly, during inspiration, nitric oxide was delivered from a gas tank containing nitric oxide 600 vpm in nitrogen (Messer Griesheim, Rheinfelden, Germany) and fed into the inspiratory limb of the ventilator tubing, 90 cm proximal of the Y-piece. A magnetic valve connected to the ventilator allowed flow of nitric oxide–nitrogen only during inspiration. Nitric oxide and nitrogen dioxide concentrations were measured by a chemiluminescent analyser (Al Med 700, ECO Physics, Dürnten, Switzerland) connected to the inspiratory limb of the ventilator tubing, 40 cm proximal of the Y-piece. After baseline measurements, four inspiratory nitric oxide concentrations (1, 10, 20 and 40 vpm) were administered in random order. Haemodynamic and gas exchange variables were measured at each nitric oxide concentration after an equilibration period of 30 min. Thirty minutes after cessation of inhalation of nitric oxide, measurements were repeated. Methaemoglobin was measured photometrically.

Patients were classified as responders (n=8) when PCP decreased by at least 2 mm Hg after nitric oxide 20 vpm. In non-responders (n=11), PCP decreased by less than 2 mm Hg at nitric oxide 20 vpm.

Data are expressed as mean (SD) unless otherwise indicated. The effects of nitric oxide on haemodynamic and gas exchange variables, except for pre- and post-capillary pressure gradients and PVR_{art} and PVR_{ven}, respectively, were analysed using two-way analysis of variance (ANOVA) for repeated measurements with one within-subject factor (nitric oxide concentration) and one between-subject factor (responder and non-responder). The effect of different nitric oxide concentrations on pre- and post-capillary pressure gradients, and on PVR_{art} and PVR_{ven} were analysed by ANOVA for repeated measurements with two within-subject factors (nitric oxide concentration and localization, i.e. pre-capillary and post-capillary) and one between-subject factor (responder and non-responder). The incidence of additional organ failures and laboratory findings of responders and non-responders were compared by one-way ANOVA. $P<0.05$ was considered statistically significant.

Results

Median lung injury score in patients was 3.25 (range 2–3.5).

In eight patients, PCP decreased by at least 2 mm Hg after nitric oxide 20 vpm (responders). In

Table 2 Haemodynamic and gas exchange variables of responders and non-responders at different NO concentrations. Responders = Patients responding with a decrease in pulmonary capillary pressure of at least 2 mm Hg at inhaled nitric oxide 20 vpm, non-responders = patients with a decrease in pulmonary capillary pressure of less than 2 mm Hg at inhaled nitric oxide 20 vpm, NO = inhaled nitric oxide, PAP = mean pulmonary artery pressure, PCP = pulmonary capillary pressure, PAWP = pulmonary artery wedge pressure, CO = cardiac output, PVR = pulmonary vascular resistance, Pa_{O_2}= arterial oxygen tension, FI_{O_2}= fraction of inspired oxygen, Pa_{CO_2}= arterial carbon dioxode tension, MAP = mean arterial pressure, CVP = central venous pressure, HR = heart rate, PEEP = positive end-expiratory pressure. Values are means (SD). *$P < 0.05$ *vs* pre-NO; †$P < 0.05$ *vs* preceeding NO concentration; ‡$P < 0.05$ *vs* non-responders at the same NO- concentration

	Responders (n=8)					
NO (vpm)	0 (pre-NO)	1	10	20	40	0 (post-NO)
PAP (mm Hg)	39 (5)	36 (6)*	35 (5)*	34 (5)*	34 (6)*	38 (5)
PCP (mm Hg)	28 (4)‡	26 (4)*	25 (4)*	23 (4)*†	24 (4)*	27 (4)
PAWP (mm Hg)	15 (3)	15 (3)	16 (3)	15 (3)	15 (3)	15 (3)
CO (litre min^{-1})	9.0 (2.9)	8.8 (2.7)	9.2 (3.2)	9.1 (2.7)	8.9 (2.6)	8.6 (2.3)
PVR (dynes s cm^{-5})	233 (70)	209 (68)*	185 (69)*	178 (73)*	178 (67)*	220 (64)
Pa_{O_2}/FI_{O_2} (kPa)	16.6 (5.7)	18.3 (7.1)*	19.7 (7.1)*	19.2 (7.6)*	18.2 (7.2)*	16.3 (6.5)
Pa_{CO_2} (kPa)	6.5 (1.0)	6.3 (0.8)	6.2 (1.0)	6.0 (1.2)	6.1 (1.0)	6.3 (0.9)
MAP (mm Hg)	87 (13)	83 (14)	82 (12)	77 (17)	78 (15)	82 (14)
CVP (mm Hg)	19 (5)	17 (4)	17 (4)	17 (3)	17 (4)	17 (4)
HR (beat min^{-1})	111 (13)	105 (17)	108 (17)	108 (17)	108 (16)	108 (17)
PEEP (mbar)	12 (2)	12 (2)	12 (2)	12 (2)	12 (2)	12 (2)
	Non-responders (n=11)					
PAP (mm Hg)	34 (5)	34 (6)	32 (5)	32 (5)	32 (4)	35 (5)
PCP (mm Hg)	22 (3)	22 (4)	22 (3)	22 (3)	22 (3)	23 (4)
PAWP (mm Hg)	15 (2)	16 (3)	16 (3)	16 (3)	16 (3)	16 (4)
CO (litre min^{-1})	8.2 (2.7)	8.4 (2.3)	8.3 (2.3)	8.3 (2.4)	8.3 (2.2)	8.2 (2.4)
PVR (dynes s cm^{-5})	197 (60)	176 (59)*	167 (52)*	166 (49)*	160 (43)*	202 (71)
Pa_{O_2}/FI_{O_2} (kPa)	16.4 (5.8)	18.2 (8.1)*	18.8 (7.3)*	20.1 (8.1)*	19.9 (8.2)*	17.5 (8.5)
Pa_{CO_2} (kPa)	5.9 (1.1)	6.0 (1.1)	5.9 (1.1)	5.9 (1.3)	5.8 (1.1)	5.9 (1.1)
MAP (mm Hg)	80 (16)	84 (10)	83 (12)	82 (10)	84 (11)	84 (12)
CVP (mm Hg)	16 (6)	17 (8)	17 (6)	16 (5)	17 (6)	17 (6)
HR (beat min^{-1})	112 (18)	110 (18)	109 (19)	108 (18)	107 (19)	107 (18)
PEEP (mbar)	11 (2)	11 (2)	11 (2)	11 (2)	11 (2)	11 (2)

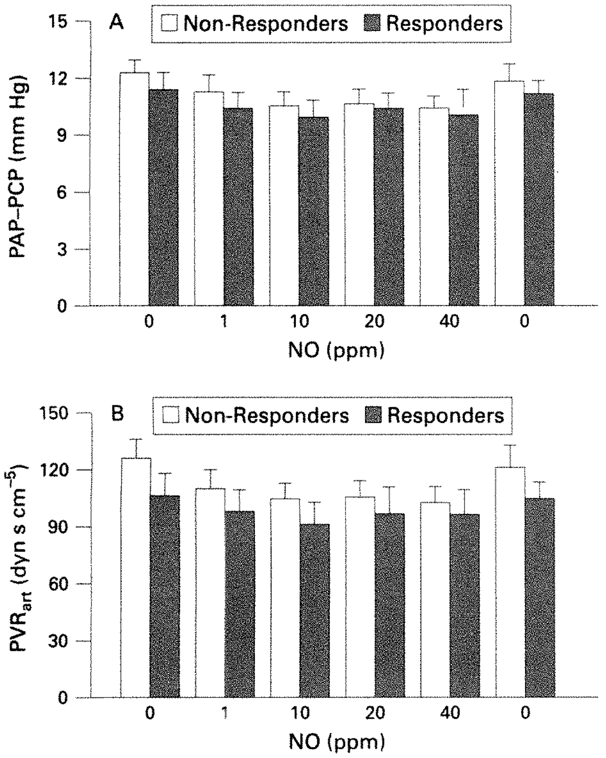

Figure 2 Pre-capillary pressure gradient (PAP–PCP) (A) and pre-capillary vascular resistance (PVR_{art}) (B) in responders (n=8) and non-responders (n=11) during inhalation of different nitric oxide concentrations (mean (SEM)). In both groups, PAP–PCP and PVR_{art} decreased slightly but not significantly during administration of nitric oxide. There were no significant differences between responders and non-responders.

the remaining 11 patients, PCP decreased by less than 2 mm Hg after nitric oxide 20 vpm (non-responders).

In responders, PAP, PCP and total PVR decreased during inhalation of nitric oxide (table 2), with a maximum effect at nitric oxide 20 vpm. PAWP and cardiac index remained constant (table 2). PAP–PCP and PVR_{art} decreased slightly after nitric oxide 1 vpm (ns), with no further decline at higher nitric oxide concentrations (fig. 2A, B). PCP–PAWP and PVR_{ven} decreased dose-dependently at nitric oxide concentrations up to 20 vpm (fig. 3A, B). The contribution of PVR_{ven} to total PVR decreased with increasing concentration of inhaled nitric oxide and was different from baseline at 20 and 40 vpm (fig. 4). The mean increase in Pa_{O_2}/FI_{O_2} was highest at 1 vpm with a further slight increase at 10 vpm (table 2). Values before and after administration of nitric oxide were not different.

In non-responders, PAP at baseline was slightly but not significantly lower than in responders (table 2). Inhalation of nitric oxide did not influence PAP. PCP at baseline was lower than in responders (22 *vs* 28 mm Hg; $P<0.05$) (table 2) and did not change at either nitric oxide concentration (table 2). Longitudinal distribution of PVR did not change during nitric oxide inhalation (fig. 4). Changes in Pa_{O_2}/FI_{O_2} were similar to those of PCP responders (table 2).

Whereas PAP–PCP and PVR_{art} of non-responders were similar to corresponding values of responders at either nitric oxide concentration (fig. 2A, B), PCP–PAWP and PVR_{ven} of non-responders were lower at baseline and at nitric oxide 1 and 10 vpm compared with responders (fig. 3A, B).

APACHE II scores (18.4 (3.3) in responders *vs* 17.3 (4.0) in non-responders), and incidence of additional organ failures, that is liver dysfunction (five of eight responders *vs* five of 11 non-responders), renal dysfunction (two of eight responders *vs* two of 11 non-responders), coagulation disorders (five of eight responders *vs* seven of 11 non-responders), host defence failure (none of all

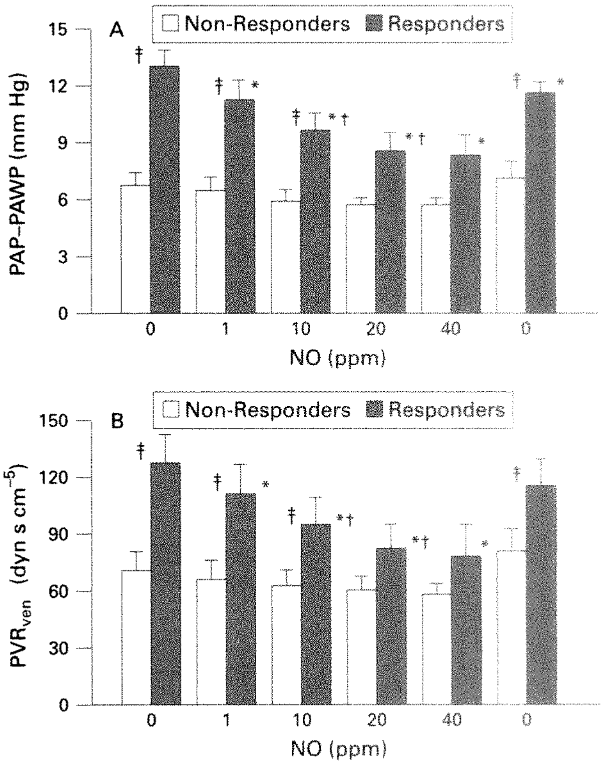

Figure 3 Post-capillary pressure gradient (PCP–PAWP) (A) and post-capillary vascular resistance (PVR_{ven}) (B) in responders (n=8) and non-responders (n=11) during inhalation of different nitric oxide concentrations (mean (SEM)). In responders, PCP–PAWP and PVR_{ven} decreased dose-dependently up to concentrations of nitric oxide 20 vpm, whereas in non-responders nitric oxide did not change PCP–PAWP or PVR_{ven}. At nitric oxide 0, 1, and 10 vpm, values of responders were significantly higher than those in non-responders (for statistical comparison see table 3). $^*P<0.05$ *vs* 0 vpm; $^†P<0.05$ *vs* preceding NO concentration; $^‡P<0.05$ *vs* non-responders at the same nitric oxide concentration.

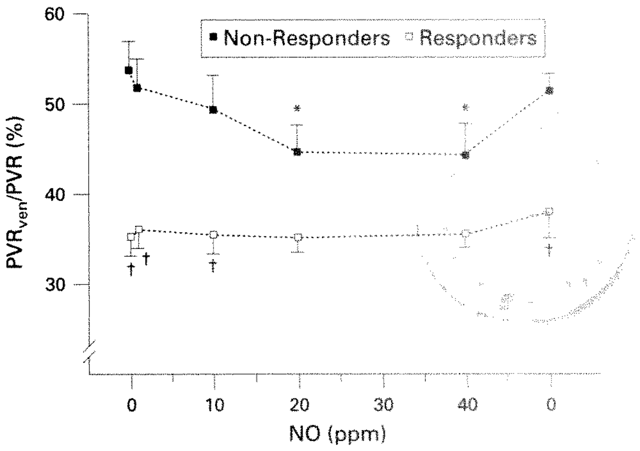

Figure 4 Contribution of post-capillary vascular resistance to total vascular resistance (PVR_{ven}) in responders (n=8) and non-responders (n=11) during inhalation of different nitric oxide concentrations (mean (SEM)). In responders, PVR_{ven} decreased during inhalation of nitric oxide with a maximum at 20 vpm. In non-responders, PVR_{ven} remained unchanged. $^*P<0.05$ *vs* 0 vpm; $^†P<0.05$ *vs* responders at the same nitric oxide concentration.

patients) and cardiovascular failure (five of eight responders *vs* seven of 11 non-responders) at the time of study were not different between responders and non-responders. Leucocyte count in peripheral blood was higher in responders compared with non-responders (19 055 (7060) mm^{-3} *vs* 9609 (5359) mm^{-3}; $P<0.005$). A positive bacteriological finding in tracheal aspirates was present in one of 11 non-responders and in five of eight responders ($P<0.02$).

Methaemoglobin concentration did not exceed 1.5%. Nitrogen dioxide concentrations (vpm) were 0.03 (0.01) at nitric oxide 1 vpm, 0.28 (0.03) at nitric oxide 10 vpm, 0.5 (0.04) at nitric oxide 20 vpm and 0.89 (0.08) at nitric oxide 40 vpm.

Discussion

The major findings of this study were that in a subgroup of ARDS patients (responders), nitric oxide decreased PCP in a dose-dependent manner with a maximum effect at 20 vpm. In responders, baseline capillary pressure was high compared with non-responders. Also, in responders, inhaled nitric oxide acted differently on pre- and post-capillary vasculature. In addition, nitric oxide changed the longitudinal distribution of PVR only at higher concentrations (20 vpm).

PAP is increased in ALI and ARDS because of release of vasoactive mediators, microthrombosis, vascular compression and hypoxic pulmonary vasoconstriction.[27] The sites of hypoxic pulmonary vasoconstriction and microthrombosis are pre-capillary vessels,[28 29] whereas vasoactive mediators constrict post-capillary vessels also.[3 4 6 7 9] Pulmonary venoconstriction results in an increase in PCP. In the presence of a capillary leak, as occurs in ALI and ARDS, PCP becomes the decisive determinant of fluid filtration, that is oedema formation.[2] Grimbert, Parker and Taylor have shown in acid-injured dog lungs that an increase in PCP by 3 mm Hg results in an eight-fold increase in pulmonary transvascular fluid filtration.[30] Therefore, reduction of PCP is one of the therapeutic goals in the treatment of ARDS.

Inhaled nitric oxide, a selective pulmonary vasodilator, has been shown to decrease PCP in blood-perfused rabbit lungs preconstricted with a stable thromboxane analogue,[14] in rat lungs preconstricted with endothelin[13] and in patients suffering from ALI and ARDS.[15 19 31] In both animal models of pulmonary hypertension, the NO-induced decrease in PCP was not parallelled by a change in longitudinal distribution of PVR suggesting a similar vasodilatating effect of nitric oxide on pre- and post-capillary vessels. Moreover, in isolated rabbit lung preparations, the degree of pre- and post-capillary vasodilatation did not increase with increasing nitric oxide concentration[14] whereas in isolated, endothelin preconstricted rat lungs, nitric oxide 670 vpm inhibited pre-capillary vasoconstriction slightly more than nitric oxide 170 vpm.[13] Other investigators found in isolated rabbit lungs preconstricted with a stable thromboxane analogue that inhaled nitric oxide 120 vpm decreased only pre-capillary resistance with no effect on post-capillary resistance.[32] In patients with ARDS, however, nitric oxide 40 vpm decreased post-capillary vascular resistance to a greater extent than pre-capillary resistance suggesting a predominant vasodilatating effect on post-capillary vessels.[15 19] Comparing the effects of nitric oxide 15 and 25 vpm in seven patients with ARDS, Rossetti, Guénard and Gabinski[31] found a significant decrease in PVR_{ven} only during inhalation of nitric oxide 25 vpm.

In healthy lungs, post-capillary vascular resistance accounts for approximately 40% of total vascular resistance.[33] In our patients, who responded to nitric oxide inhalation with a significant decrease in PCP, baseline contribution of post-capillary PVR to total vascular resistance was high (54%). In these patients, nitric oxide dilated post-capillary vessels dose-dependently up to 20 vpm whereas pre-capillary vascular resistance decreased slightly at 1 vpm nitric oxide. In contrast with responders, baseline PVR_{ven}/PVR of non-responders was normal (35%) and inhalation of nitric oxide did not influence longitudinal distribution of PVR.

The different findings between animal studies and patients with ALI and ARDS may be explained by species differences and characteristics of the animal models.[34 35]

Inhaled nitric oxide dilates preconstricted pulmonary vessels but has no effect on vessels at normal tone.[11 36] In isolated rabbit lungs, infusion of a thromboxane analogue caused a marked increase in pre-capillary resistance. In contrast, the increase in post-capillary resistance was relatively small.[14] In isolated rat lungs, endothelin-induced vasoconstriction was more pronounced in pre-capillary than in post-capillary vessels.[13] Reversing flow in thromboxane preconstricted rabbit lungs resulted in a marked increase in pulmonary venous resistance.[32] Under those circumstances, inhaled nitric oxide dilated post-capillary vessels. In KCL preconstricted bovine pulmonary vessels, nitric oxide dilated veins more than arteries.[37]

Thus the different effects of inhaled nitric oxide in this study may be the result of a variable degree of pulmonary venoconstriction in patients with ARDS. Longitudinal distribution of PVR tends to normalize during inhalation of nitric oxide. When pulmonary venoconstriction is pronounced, inhalation of nitric oxide results in a marked venodilatation with a concomitant decrease in PCP. In that instance, higher nitric oxide concentrations (20 vpm) are necessary for optimal venodilatation.

In our study, responders and non-responders were not different with regard to gas exchange, cardiac output, ventricular filling pressures, APACHE II score[24] or incidence of organ dysfunction.[25] In our small group of patients the underlying disease did not influence the response to inhaled nitric oxide. Leucocyte count, however, was higher in responders than in non-responders. In isolated, TNFα-challenged guinea pig lungs, perfusion with neutrophil enriched perfusate increased PCP from 6.0 to 12.8 cm H_2O.[38] Post-capillary vascular resistance increased from 0.075 to 0.339 cm H_2O ml^{-1} min^{-1} whereas pre-capillary resistance was unchanged.[38] In isolated rat lungs, perfusion with PMA-activated leucocytes resulted in pulmonary hypertension and an increase in PCP.[39] Post-capillary resistance increased significantly but the increase in pre-capillary vascular resistance was not significant. Thus in our patients leucocytes may have contributed to the differences in longitudinal distribution of PVR values of responders and non-responders.

The effect of nitric oxide on pre-capillary vascular resistance was relatively small. The small decrease in PVR_{art} during inhalation of nitric oxide may be the result of a relatively modest vasoconstriction of pre-capillary vessels. Moreover, as nitric oxide inactivation by haemoglobin is inversely related to oxygen saturation,[40] nitric oxide may be inactivated more effectively in pre-capillary than in post-capillary vessels.

A possible limitation of our study was the technique used to estimate PCP. Standard techniques for measurement of PCP are micropuncture[41] and the isogravimetric method.[42] Vascular occlusion methods correlate well with the isogravimetric method for measuring microvascular pressure in isolated lung preparations.[43–45] These methods,[41–45] however, cannot be applied to intact lungs. Analysis of PAP decay after balloon inflation has been used in intact lungs under the premise that balloon inflation in the *in situ* lung is equivalent to arterial occlusion in the isolated lung.[26 43] Although it has been demonstrated that analysis of the pressure decay curve appears to be a valid method for estimating PCP[26 43 45] and that visual analysis of the pressure decay curve is an adequate approach for estimating PCP,[26 46] analysis of pressure decay profiles remains a subject of debate.[47 48]

This study may have clinical implications. In the presence of a capillary leak, PCP is the major factor determining transvascular fluid filtration.[2] Inhaled nitric oxide has been shown to reduce transvascular fluid flux in rabbit lungs with oxidant-induced lung injury,[16] in isolated rat lungs with neutrophil-mediated capillary leak[17] and in hydrogen peroxide challenged rabbit lungs.[18] In patients with ALI, nitric oxide 40 vpm inhibited transvascular albumin flux.[19] The decrease in transvascular albumin flux correlated well with the NO-induced decrease in PVR_{ven}. As we have now demonstrated that PCP decreases with nitric oxide 10 and 20 vpm, transvascular fluid flux may be reduced at nitric oxide concentrations lower than 40 vpm. A dose–response of nitric oxide on transvascular flux has yet to be established.

The maximal effect of nitric oxide on Pa_{O_2}/FI_{O_2} was observed at 1 vpm with a further slight but insignificant increase at 10 and 20 vpm. This finding is in agreement with previous studies.[21 22 49 50] It is worth noting that the maximum effect of inhaled nitric oxide on PVR_{art} and on Pa_{O_2}/FI_{O_2} was achieved at 1 vpm. As pre-capillary vessel tone is involved in the regulation of blood supply to the alveoli, it is possible that the increase in Pa_{O_2} depends on the pre-capillary vasodilating action of nitric oxide.

The observed nitrogen dioxide concentrations after nitric oxide 10 and 20 vpm may have clinically relevant side effects in some patients.[51] Therefore, when administering nitric oxide concentrations of 10–20 vpm for prolonged periods, we would recommend nitrogen dioxide scavenging.

In summary, we found that in patients with ARDS, inhaled nitric oxide changed longitudinal distribution of PVR and decreased PCP when post-capillary vascular resistance was high. The maximum effect was achieved at nitric oxide 20 vpm.

Acknowledgement

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Influence of surgical technique on early postoperative hypoxaemia in children undergoing elective palatoplasty

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Summary

We have assessed the influence of different surgical procedures on the incidence, severity and duration of early postoperative hypoxaemia in 312 healthy infants and children undergoing elective palatoplasty. Group 1 patients underwent von Langenbeck palatoplasty (n=149), group 2 patients underwent push-back palatoplasty (n=124) and group 3 patients underwent combined push-back palatoplasty and superior pharyngeal flap surgery (n=39). Arterial oxygen saturation (Sp_{O_2}) was recorded while patients were breathing air shortly after arrival in the recovery room (0 min), and at 5, 10, 15, 20, 30, 40, 50, 60, 120 and 180 min thereafter. Patients who underwent more complex surgical techniques for palatoplasty had lower postoperative Sp_{O_2} values, slower recovery of Sp_{O_2} and a higher incidence of hypoxaemia during the early postoperative period. There were significant differences in postoperative Sp_{O_2} values and the incidence of hypoxaemia. The incidences of hypoxaemia and severe hypoxaemia were 27% and 1%, respectively, in group 1, 37% and 12% in group 2, and 36% and 33% in group 3. Hypoxaemia occurred most commonly in the first 15 min in children after von Langenbeck palatoplasty, in the first 40 min after push-back palatoplasty and in the 120 min after combined push-back palatoplasty and superior pharyngeal flap surgery. There were significant associations between low Sp_{O_2} values, incidence of hypoxaemia on admission to the recovery room and recovery scores. (*Br. J. Anaesth.* 1998; **80**: 447–451)

Keywords. hypoxaemia; anaesthesia, paediatric; surgery, postoperative period; surgery, plastic

Patients undergoing elective palatoplasty are at increased risk of early postoperative hypoxaemia. Surgery can cause airway compromise from oedema of the palate, pharynx or tongue, and thickened secretions or blood in the pharynx.[1 2] The patient may also be unable to clear pulmonary and oral secretions. Most patients undergoing palatoplasty are infants or children. They have a relatively higher oxygen consumption compared with adults,[3] but may also be at increased risk of airway closure during tidal breathing because the elastic recoil pressure of the lungs and thorax is low and closing capacity is increased.[4] A previous study showed that hypoxaemia was more common and more severe in children undergoing cleft palate repair than other types of plastic surgery.[5] However, there are no data on the influence of surgical technique on postoperative hypoxaemia in infants and children after palatoplasty. We studied the features of early postoperative hypoxaemia in healthy infants and children undergoing different forms of palatoplasty.

Patients and methods

We studied 312 infants and children, ASA I, aged 8 months to 14 yr, undergoing elective palatoplasty. The study was approved by the Institutional Human Study Committee and informed consent was obtained from parents. Children with a history of recent respiratory tract infection, cardiac or lung diseases or those with anaemia were excluded. Patients were divided into three groups according to the surgical procedure: group 1 patients underwent van Langenbeck palatoplasty, group 2 patients had push-back palatoplasty and group 3 patients, combined push-back palatoplasty and superior pharyngeal flap surgery. Patient characteristics are shown in table 1.

Diazepam 0.2 mg kg^{-1} (maximum 10 mg) and scopolamine 5 μg kg^{-1} were given i.m., 1 h before anaesthesia. Anaesthesia was induced with thiopental 4–6 mg kg^{-1} i.v., fentanyl 2 μg kg^{-1} i.v. and succinylcholine 1.5 mg kg^{-1} i.v., followed by tracheal intubation. Anaesthesia was maintained with 1–2% enflurane (expired concentration) and 67% nitrous oxide in oxygen, and vecuronium or pancuronium was given for neuromuscular block. Thiopental 2 mg kg^{-1} or fentanyl 2 μg kg^{-1} was supplemented i.v. as required. The lungs were ventilated and $P\text{E}'_{CO_2}$ was kept within normal limits. Inspired and end-tidal concentrations of oxygen, carbon dioxide, nitrous oxide and enflurane were measured and displayed digitally (Anaesthesia Gas Monitor Type 1304, Bruel and Kjaer, Denmark). Sp_{O_2} was monitored by a Datex pulse oximeter (Model CH-S-23, Datex Instrumentarium, Helsinki, Finland).

During surgery, the child's head was placed at the top of the operating table with the neck in moderate hyperextension and a 15° Trendelenburg tilt. A Dingman mouth gag was inserted to provide surgical

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exposure. Lidocaine 0.25% with epinephrine 1:200 000 was infiltrated into the operative site before incision to provide haemostasis. In the von Langenbeck operation, the mucous membrane of the hard palate and underlying periosteum are stripped off the bone as a single layer. The edges of the cleft are pared and the soft tissues of the two halves of the palate—that is, the mucoperiosteum anteriorly and the soft palate posteriorly—are slid towards each other and stitched in the midline. To allow this to happen, release incisions have to be made on each side and these run just inside the alveolar process from the region of the canine anteriorly, curving round the maxillary tuberosity, to end just behind the region of the pterygoid hamulus. The mucoperiosteum is then elevated from the bone as a bipedicled flap, attached anteriorly and posteriorly, and dissection is carried out through the posterior ends of release incisions to relax the soft palate. The push-back operation commences in the same way as the von Langenbeck, with raising of the mucoperiosteal flap, and similar release incisions are made laterally. However, the anterior ends of the lateral incisions are joined to the margins of the cleft by oblique cuts which produce three flaps in the incomplete cleft or four in the complete cleft. The palate can be lengthened by freeing the two posterior mucoperiosteal flaps so that they can slide backwards. This is done by freeing the aponeurotic and muscular attachments of the soft palate from the back of the hard palate, and undermining the nasal mucosa as far as possible from the upper surface of the hard palate. In patients in group 3, a superior pharyngeal flap is made and is inset posteriorly into the soft palate as an obturator after the push-back operation is finished. Minimal or moderate blood loss was usually replaced with crystalloid solution during surgery.

At the end of anaesthesia, all children breathed 100% oxygen for at least 5 min after nitrous oxide was discontinued. If residual neuromuscular block was detected by thenar muscle response, it was antagonized with atropine 0.03 mg kg^{-1} and neostigmine 0.07 mg kg^{-1} i.v. If ventilation was suspected to be depressed as a result of intraoperative administration of fentanyl (i.e. ventilatory frequency less than 12 bpm while tidal volume was well sustained) naloxone 1 μg kg^{-1} was given i.v. When protective reflexes recovered and spontaneous breathing was re-established (tidal volume >5 ml kg^{-1}, ventilatory frequency >l2 bpm), that is when children breathed room air for at least 3 min and Sp_{O_2} was maintained at ≥90%, or when the child was awake, tracheal extubation was performed and 100% oxygen was administered via a face mask for 3–5 min before transfer to the recovery room in a 5° head-down position. Respiratory status was observed and recorded in the recovery room. Adequacy of ventilation was assessed clinically by observing expiratory airflow from the nose or mouth and movement of the thorax with or without auscultation with a stethoscope. Airway obstruction was scored as follows: (1) absent, (2) mild (light snoring with adequate ventilation), (3) moderate (necessitating a change in position or oropharyngeal airway) and (4) severe (obstructive apnoea or heavy snoring with ventilatory disturbances or requiring re-intubation). Sp_{O_2} values were recorded shortly after arrival in the recovery room (0 min) and at 5, 10, 15, 20, 30, 40, 50, 60, 120 and 180 min thereafter. Sp_{O_2} values ≤90% were classified as hypoxaemia and ≤85% as severe hypoxaemia.[6] If Sp_{O_2} values decreased to 85%, 100% oxygen was administered immediately via a face mask.

A modified Aldrete scoring system[7] was used to evaluate recovery from anaesthesia. Scoring included level of motor activity, respiration, arterial pressure, consciousness and colour on admission to the recovery room and at frequent intervals thereafter. To investigate the association between patient recovery scores and incidence and severity of early postoperative hypoxaemia, patients in each group were further divided into two recovery groups: (1) those with a low recovery score (score ≤6) and (2) those with a high recovery score (score 7–10).

All data were analysed using POMS statistical software, version 2.00 (Shanghai Scientific and Technical Publishers, Shanghai, People's Republic of China). Comparisons of Sp_{O_2} values and patient data between groups were made using one-way analysis of variance, and comparisons of Sp_{O_2} values within groups were performed using repeated measures analysis of variance. Where the calculated F value exceeded the critical value for the 0.05 probability level, the Student–Newman–Keuls test was used to determine which differences were significant. Sp_{O_2} values were compared using the Student's t test between children with a low (score ≤6) and a high (score 7–10) recovery score in each group. Comparisons of the incidence of hypoxaemia between and within groups, and comparisons of the incidence of airway obstruction between groups were performed using a chi-square test. The Bonferroni correction was used when multiple comparisons were performed. The relationships between Sp_{O_2} values on arrival in the recovery room and recovery scores were analysed by linear regression analysis. $P<0.05$ was considered significant.

Results

Surgical procedures in all the children were uneventful and blood loss was minimal (mean blood

Table 1 Patient characteristics (mean (SD or range)). $^{*}P<0.05$ compared with group 1; $^{\dagger}P<0.05$ compared with group 2

	Group 1 (n=149)	Group 2 (κ=124)	Group 3 (n=39)*
Age (yr)	3.2 (0.75–6)	3.5 (1.8–12)	4.2 (2.1–14)*
Weight (kg)	12.2 (4.5)	13.5 (5.1)	15.5 (5.6)*
Height (cm)	101.7 (15.4)	105.8 (18.2)*	107.7 (17.4)*
Temperature (°C)	36.5 (0.2)	36.4 (0.1)	36.6 (0.2)
Haemoglobin (g dl^{-1})	13.2 (5)	12.8 (1.4)	12.9 (1.3)
Duration of surgery (h)	1.8 (1.1)	2.7 (1.8)*	3.5 (1.4)*†
Transfer time (s)	93.4 (18.7)	92.3 (21.2)	91.1 (14.7)
Fentanyl dose (μg kg^{-1})	5.5 (2.6)	7.1 (3.2)*	8.9 (3.5)*†

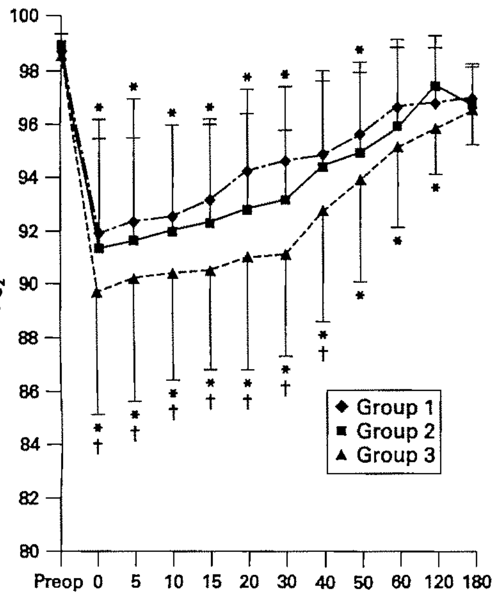

Figure 1 Postoperative Sp_{O_2} values in children in the 3 h after cleft palate repair following the three surgical techniques: group 1, von Langenbeck palatoplasty; group 2, push-back palatoplasty; group 3, combined push-back palatoplasty and superior pharyngeal flap surgery. Values are mean (SD). *$P<0.05$, groups 2 and 3 *vs* group 1; †$P<0.05$, group 3 *vs* group 2.

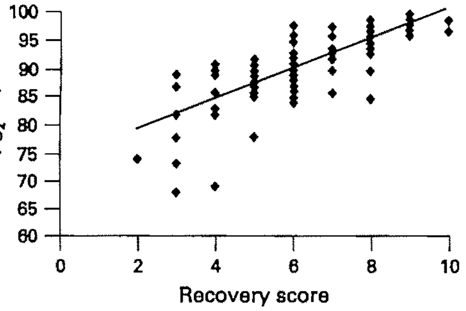

Figure 2 Correlation between Sp_{O_2} values on arrival in the recovery room and recovery scores. The linear regression equation related to the recovery scores as follows: Sp_{O_2} (%)=76.7±2.32 × recovery scores, $r=0.81$, $P<0.0001$.

loss 57 (SD 25) ml; no significant differences between groups). Before extubation, naloxone was required to reverse suspected respiratory depression as a result of fentanyl administration in three children in group 1 (2%), in six in group 2 (5%) and in four in group 3 (10.3%) (group 1 *vs* group 3, $P<0.05$). On arrival in the recovery room, 102 children had mild upper airway obstruction. The incidences of mild upper airway obstruction in groups 1, 2 and 3 were 25%, 39% and 44%, respectively (group 1 *vs* group 2 or 3, and group 2 *vs* group 3, $P<0.05$). Fifty-one children had moderate airway obstruction, of whom 13 required an oropharyngeal airway. The incidences of moderate upper airway obstruction in groups 1, 2 and 3 were 3.4%, 27% and 41%, respectively (group 1 *vs* group 2 or 3, and group 2 *vs* group 3, $P<0.05$). No patient had severe airway obstruction or required tracheal re-intubation. Opioid analgesics and sedative drugs were not given throughout the study.

Sp_{O_2} values while breathing room air decreased significantly after surgery in all patients and then increased gradually. In the early postoperative period, the degree of arterial desaturation and incidence of hypoxaemia were closely related to the surgical technique for palatoplasty, being greatest for combined push-back palatoplasty and superior pharyngeal flap, less for push-back surgery and least for the von Langenbeck operation. Sp_{O_2} values and incidence of hypoxaemia in the early postoperative period were significantly different between the three groups (fig. 1, table 2).

Table 2 Incidences of hypoxaemia and severe hypoxaemia in the first 3 h after arrival in the recovery room (No. (% incidence) of patients). *$P<0.05$ compared with 0 min; †$P<0.05$ compared with group 1; ‡$P<0.05$ compared with group 2

	Group 1 (n=149)	Group 2 (n=124)	Group 3 (n=39)
0 min			
Sp_{O_2}=86–90%	40 (27)	46 (37)	12 (31)
$Sp_{O_2}\leqslant$85%	2 (1)	15 (12)†	13 (33)†‡
Total episodes	42 (28)	61 (49)†	25 (64)†
5 min			
Sp_{O_2}=86–90%	35 (23.5)	42 (34)†	14 (36)†‡
$Sp_{O_2}\leqslant$85%	1 (0.7)	11 (9)†	12 (31)†‡
Total episodes	36 (24.2)	53 (43)†	26 (67)†‡
10 min			
Sp_{O_2}=86–90%	20 (13.4)*	36 (29)†	13 (33)†
$Sp_{O_2}\leqslant$85%	0 (0)	8 (6.5)†	10 (26)†‡
Total episodes	20 (13.4)*	44 (35.5)*†	23 (59)†‡
15 min			
Sp_{O_2}=86–90%	15 (10)*	31 (25)*†	13 (33)†
$Sp_{O_2}\leqslant$85%	0 (0)	5 (4)*†	8 (21)†‡
Total episodes	15 (10)*	36 (29)*†	21 (54)†‡
20 min			
Sp_{O_2}=86–90%	8 (5.4)*	28 (22.6)*†	12 (31)†
$Sp_{O_2}\leqslant$85%	0 (0)	2 (1.6)*	5 (13)*†‡
Total episodes	8 (54.4)*	30 (24.2)*†	17 (44)†‡
30 min			
Sp_{O_2}=86–90%	6 (4)*	21 (16.9)*†	11 (28.2)†
$Sp_{O_2}\leqslant$85%	0 (0)	1 (0.8)*	4 (10.3)*†‡
Total episodes	6 (4)*	22 (17.7)*†	15 (38 5)*†‡
40 min			
Sp_{O_2}=86–90%	4 (2.7)*	12 (9.7)*†	10 (26)†
$Sp_{O_2}\leqslant$85%	0 (0)	1 (0.8)*	4 (10)*†‡
Total episodes	4 (2.7)*	13 (10.5)*†	14 (36)*†‡
50 min			
Sp_{O_2}=86–90%	2 (1.3)*	6 (4 8)*	7 (18)†‡
$Sp_{O_2}\leqslant$85%	0 (0)	1 (0.8)*	2 (5)*†
Total episodes	2 (1.3)*	7 (5.6)*†	9 (23)*†‡
60 min			
Sp_{O_2}=86–90%	1 (0 7)*	3 (2.4)*	5 (13)†‡
$Sp_{O_2}=\leqslant$85%	0 (0)	0 (0)*	2 (5)*†
Total episodes	1 (0.7)*	3 (2.4)*	7 (18)*†‡
102 min			
Sp_{O_2}=86–90%	0 (0)*	1 (0.8)*	2 (5)*†
$Sp_{O_2}\leqslant$85%	0 (0)	0 (0)*	1 (3)*
Total episodes	0 (0)*	1 (0.8)*	3 (8)*†‡
180 min			
Sp_{O_2}=86–90%	0 (0)*	0 (0)*	1 (3)*
$Sp_{O_2}\leqslant$85%	0 (0)	0 (0)*	0 (0)*
Total episodes	0 (0)*	0 (0)*	1 (3)*

The recovery rate of postoperative Sp_{O_2} was most rapid from 0 to 30 min in children after von Langenbeck palatoplasty, with a mean net increase of 2.7% over 30 min. However, the recovery rate of Sp_{O_2} was most rapid from 30 to 60 min in children after push-back palatoplasty or combined push-back palatoplasty and pharyngeal flap surgery, with mean net increases of 2.8% and 3.0%, respectively (fig. 1). Sp_{O_2} values in all patients reached more than 90% by 69 min after admission to the recovery room in group 1, by 145 min in group 2 and by 210 min in group 3. However, mean Sp_{O_2} values were lower than baseline in all patients, even at 180 min after operation.

The incidence of hypoxaemia and Sp_{O_2} values on arrival in the recovery room were also related to recovery scores (table 3). A significant correlation was found between postoperative Sp_{O_2} and recovery scores (fig. 2).

Discussion

This study has demonstrated that more than one-third of patients undergoing palatoplasty became hypoxaemic after surgery. The cause of this hypoxaemia is probably multifactorial.[8–11] It may be related to the anaesthetic itself, as it is an extension of the gas exchange that occurs during anaesthesia. Alveolar hypoventilation, ventilation–perfusion mismatch, right to left shunting of blood, decreased cardiac output and increased oxygen consumption caused by hypertonic muscles and shivering are potential causative factors.[9] The normal hypoxic drive to ventilation may be abolished by concentrations of enflurane as low as 0.1 MAC.[11] This concentration may be present in the immediate postoperative period and may cause early phase respiratory depression. Diffusion hypoxia after nitrous oxide is unlikely to be a contributing factor as all children breathed 100% oxygen for at least 5 min at the end of operation. The residual effects of neuromuscular block could aggravate early postoperative hypoxaemia, but routine antagonism of residual neuromuscular block at the end of surgery make this unlikely.

Except for the effects of anaesthesia on respiratory function described above, patients undergoing palatoplasty are at risk of upper airway obstruction because of block of the nasal airway and oedema of the palate, pharynx or tongue.[1] Secretions or blood in the pharynx can increase the degree of upper airway compromise, especially in young children with smaller airways.

Arterial desaturation and the incidence of hypoxaemia were related closely to the surgical technique for palatoplasty. There are several reasons for this. Compared with von Langenbeck palatoplasty, after push-back palatoplasty and combined push-back palatoplasty and superior pharyngeal flap surgery, children are more susceptible to upper airway obstruction during the early postoperative period. The incidence of mild and moderate upper airway obstruction is greatest for combined push-back palatoplasty and superior pharyngeal flap, less for push-back surgery and least for von Langenbeck operation. This may be related to a greater degree of velopharyngeal space contraction in push-back surgery and part naso-airway obstruction in pharyngeal flap surgery. Patients with more airway compromise may be more susceptible to residual anaesthetic effects.[12] In addition, more complex surgical techniques for palatoplasty imply a longer procedure, longer retractor time, more difficult repair and perhaps other co-existing pathology.

Previous studies showed that the duration of mouth-gag use strongly correlated with the incidence and severity of airway compromise.[1, 11] The incidence of postoperative airway obstruction increased 10-fold if the duration of the procedure was more than 2 h.[13] The development of tongue swelling appears to be related to the duration of repair of the cleft palate.[14–16] Swelling and oedema of the tongue may be secondary to ischaemia induced by the mouth-gag. The tongue and local tissue injury may also be exacerbated by an extreme Trendelenburg position, which compounds venous stasis and oedema. Periodic relief of pressure from the mouth gag during surgery may reduce lingual oedema.[1] This may be a reason for the lack of severe airway obstruction in our patients.

Early postoperative hypoxaemia is most likely caused by central or obstructive apnoea. Obstructive apnoea is caused by closure of the upper airway, which may occur when neural control of upper airway is impaired or abolished (as in REM sleep, during anaesthesia or during sleep after operation following administration of morphine).[17]

The effects of von Langenbeck palatoplasty on sleep-related upper airway obstruction were usually minimal and clinically insignificant, whereas severe obstructive apnoea was present in most patients after pharyngeal flap surgery. An incidence of 10–95% of significant obstructive apnoea has been noted during the early postoperative period after pharyngeal flap surgery.[2, 18, 19] Although we did not measure sleep or Pa_{CO_2} values, irregular respiration and snoring were common in our children after combined push-back palatoplasty and pharyngeal flap surgery. Therefore, we considered that obstructive apnoea was related to the highest incidence of hypoxaemia and moderate airway obstruction after combined push-back palatoplasty and pharyngeal flap surgery.

More specifically, concerning administration of fentanyl, the dose of fentanyl administered was significantly different between groups, but the suspected respiratory depression caused by fentanyl was reversed before extubation, and no child had clinical signs of respiratory depression as a result of fentanyl use in the recovery room (i.e. all children had a ventilatory frequency of 12 bpm), and opioid analgesics and sedative drugs were not used throughout the study. The recovery score is often used to evaluate the patient's degree of recovery from anaesthesia in the recovery room and to determine when the patient is ready to leave.[20] When the recovery scores were similar, the children in our study who

Table 3 Sp_{O_2} and proportion of Sp_{O_2} ≤90% and ≥91% between children with low and high recovery scores. $P<0.05$ compared with children with recovery score of: *≤6 in group 1; †7–10 in group 1; ‡≤6 in group 2; and §7–10 in group 2

	Recovery score	*n*	Sp_{O_2} (mean (SD))	Sp_{O_2}≥91% (*n* (incidence %))	Sp_{O_2}≤90%
Group 1	≤6	77	91.0 (3.8)	43 (56)	44 (44)
	7–10	72	92.8 (2.7)*	55 (76)*	17 (24)*
Group 2	≤6	55	90.6 (5.2)*	18 (33)*†	37 (67)*
	7–10	69	91.8 (3.3)†‡	51 (74)	18 (26)
Group 3	≤6	22	89.0 (5.4)*‡	6 (27)*†	16 (73)*
	7–10	17	90.6 (4.7)†§	10 (59)	7 (41)

underwent more complex surgical procedure for palatoplasty had a higher incidence of hypoxaemia and lower Sp_{O_2} values in the postoperative period compared with those who underwent a more simple surgical technique. In addition, other studies have failed to demonstrate that the use of opioids in anaesthesia is associated with an increased incidence of postoperative hypoxaemia.[21] Therefore, the differences in postoperative Sp_{O_2} values and hypoxaemia observed between groups were more likely a result of the surgical technique.

We also found a significant correlation between recovery scores and hypoxaemia and the degree of arterial desaturation during the early postoperative period, indicating that postoperative recovery of respiratory function depends on the degree of recovery from anaesthesia. This is in accordance with the results of previous studies in children.[5 22] Hypoxaemia was most frequent within 2 h after surgery, particularly in the first 15 min in children after von Langenbeck palatoplasty, in the first 40 min after push-back palatoplasty and in the first 120 min after combined push-back palatoplasty and superior pharyngeal flap surgery. During this time, patients should be monitored closely, especially those with a low recovery score. In our patients, hypoxaemia was quickly corrected by gently stimulating the child to take deep breaths and by repositioning the head, and oxygen therapy. Because of the high incidence of hypoxaemia, pulse oximetry is an essential monitor for children undergoing palatoplasty after general anaesthesia. We also recommend oxygen, at least until children are awake.[22]

In our study, Sp_{O_2} values were lower than baseline, even 3 h after operation. This may be related to administration of diazepam i.m. before operation, use of fentanyl as part of general anaesthesia and various degrees of upper airway compromise. Fentanyl is said to have a short duration of action, but it may depress respiratory function for some time.[23] Except for surgical techniques, a larger total fentanyl dose during longer surgical procedures may be another cause of slower recovery of postoperative respiratory function in children who have undergone a more complex surgical technique for palatoplasty because fentanyl depresses the susceptibility of the respiratory centre to hypercapnia and hypoxia in a dose related manner.[24]

In summary, we found that arterial desaturation and hypoxaemia were related to the surgical technique, being greatest for combined push-back palatoplasty and superior pharyngeal flap, less for push-back surgery and least for the von Langenbeck operation. There were significant associations between low Sp_{O_2} values and the incidence of hypoxaemia on admission to the recovery room and recovery scores.

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Sevoflurane compared with halothane for tracheal intubation in children

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Summary

We have studied 40 healthy children, aged 3–10 yr, undergoing adenotonsillectomy, in a double-blind, randomized study. Intubating conditions were assessed when the pupils had become small and central after inhalation induction with either 5% halothane and 60% nitrous oxide in oxygen or 8% sevoflurane and 60% nitrous oxide in oxygen. The quality of tracheal intubation was graded according to ease of laryngoscopy, position of the vocal cords, coughing, jaw relaxation and movement of limbs. Fewer children had significant vocal cord movement on laryngoscopy ($P<0.01$) and more had ideal intubating conditions when halothane was used (12 of 20 compared with seven of 20; ns). Time to reach the clinical end-point for intubation was reached sooner with halothane ($P=0.015$). In all children the trachea was intubated successfully at the first attempt and all remained haemodynamically stable throughout induction. (*Br. J. Anaesth.* 1998; **80**: 452–455)

Keywords: intubation tracheal; anaesthesia, paediatric; anaesthetic techniques, induction; anaesthetics volatile, halothane; anaesthetics volatile, sevoflurane

Tracheal intubation may be facilitated in children by succinylcholine,[1 2] non-depolarizing neuromuscular blocking agents or by using a combination of propofol and alfentanil.[3–7] Inhalation induction is often used in paediatric practice and there is renewed interest in the technique since the introduction of sevoflurane. Sevoflurane is non-irritant to the airway, non-pungent and provides rapid induction because of its low blood:gas solubility.[8] Many studies have demonstrated the acceptability and rapidity of inhalation induction with sevoflurane in children.[9–12] The ED_{95} end-tidal sevoflurane concentration for tracheal intubation has been reported as 4.68% (mean) but with wide 95% confidence intervals (3.91–12.74%).[13 14] The decision on when the child is ready for intubation is based on clinical indicators of depth of anaesthesia. Constriction and centralization of the pupils and the presence of a regular diaphragmatic respiratory pattern (automatic breathing) indicate that the plane of "surgical anaesthesia" has been reached.

Halothane has been used worldwide for many years and provides smooth inhalation induction and good intubating conditions. It remains the intubating agent of choice for the difficult airway but may produce myocardial depression and cardiac arrhythmia. It undergoes significant metabolic breakdown and may cause the rare, but serious, complication of hepatitis.[15 16] Intubating conditions have been compared after inhalation induction with halothane and sevoflurane in one Japanese study[17] but assisted ventilation via a face mask was used before intubation. Our study was designed to assess the performance of the two agents in elective cases while maintaining spontaneous respiration before a formal assessment in children with airway compromise. Our aim was to mimic as far as possible the technique which would be used in children with airway obstruction but ethical considerations determined that we had to include nitrous oxide in the induction gas mixture.

Patients and methods

After obtaining local Ethics Committee approval and informed written consent from the parents or from the child if appropriate, we studied 40 ASA I or II children undergoing elective adenotonsillectomy. Children with significant airway, cardiac, respiratory, renal, hepatic or central nervous system diseases were excluded. No child had received a general anaesthetic within the past 2 weeks, and any child with a history of an unusual response to a halogenated anaesthetic was excluded. Each child was allocated randomly to undergo inhalation induction with either halothane or sevoflurane using a computer-generated randomization programme (Trialaid; Dr G. Hutchison, Dundee).

All children received sedative and antiemetic premedication with trimeprazine 2 mg kg^{-1}, 1–1.5 h before induction, and EMLA cream (eutectic mixture of local anaesthetics) was applied 1 h before induction. On arrival in the induction room, initial non-invasive measurements were performed. These included: heart rate (HR), arterial oxyhaemoglobin saturation by pulse oximetry (Sp_{O_2}) and arterial pressure by automatic oscillotonometry (MAP). The arterial pressure reading was omitted before induction in some children if they found it upsetting.

Each child received inhalation induction with either halothane or sevoflurane and 60% nitrous oxide in oxygen. Incrementally increasing doses of volatile agent were used until the child was breathing 8% sevoflurane or 5% halothane. The rate of

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Table 1 Scoring system for intubating conditions[7 18]

Score	Laryngoscopy	Vocal cords	Coughing	Jaw relaxation	Limb movement
1	Easy	Open	None	Complete	None
2	Fair	Moving	Slight	Slight	Slight
3	Difficult	Closing	Moderate	Stiff	Moderate
4	Impossible	Closed	Severe	Rigid	Severe

Table 2 Patient details (mean (SD) [range] or number). No significant differences between groups

	Halothane	Sevoflurane
n	20	20
Sex (M:F)	8:12	8:12
Age (months)	69.7 [36–120]	83.7 [36–120]
Weight (kg)	21.1 (5.84) [15–35]	22.8 (5.70) [15–40]

incremental increase was determined by tolerance to the face mask which in practice implied every three breaths (an increase of 0.5% in the halothane vaporizer setting or 1% for sevoflurane). I.v. access was established and the vaporizer was covered. One of two senior anaesthetists were allowed into the induction room where they assessed continuously pupil size and position. When the pupils were deemed to be small and central, the trachea was intubated. Having entered the room only when the patients were asleep, and with all gases scavenged where possible, the intubating anaesthetist was unaware, as far as possible, of the induction agent used. We did not record the concentration of end-tidal volatile agent or time breathing the maximum available vapour concentration.

The quality of the intubating conditions was assessed and recorded immediately by the senior intubating anaesthetist. The scoring system used was that devised by Helbo-Hansen, Ravlo and Trap-Anderson[18] and revised by Steyn and colleagues.[7] Variables assessed were ease of laryngoscopy, vocal cord position, coughing on laryngoscopy or on intubation, jaw relaxation and presence or absence of limb movement on intubation. All variables were allocated a score of 1–4, with 1 being ideal conditions. Therefore, the best possible score was 5. Intubating conditions were considered unacceptable if a score of 3 or 4 was recorded in any individual category (table 1).

When the trachea was intubated, the child continued to breath 1 MAC of the volatile anaesthetic until all measurements were complete, at which point patients were transferred to the operating room and maintained on isoflurane and nitrous oxide in oxygen until the end of surgery. Opioids were administered only when recordings were complete. Recordings of HR, Sp_{O_2} and MAP were obtained when the eyelash reflex was lost, immediately after intubation, and at 1-, 2- and 3-min intervals after intubation. The study ended at this point.

STATISTICAL ANALYSIS

The chi-square test and Mann–Whitney U test were used for non-parametric data and the Student's t test for parametric data. Minitab v 11 was used for data handling and statistical analysis. Prospective power analysis (Trialaid) revealed that a group size of 16 would be required to detect a 20% difference between groups with 95% power and $P = 0.05$.

Results

The 40 children enrolled in the study were allocated equally between the halothane and sevoflurane groups. All children easily tolerated inhalation induction and all completed the study. There were no significant differences in patient characteristics between the two groups (table 2).

Intubation was successful in all children at the first attempt, without the need for other interventions, and all had grade 1 laryngoscopies. In each group, only one patient had a score of 3 in any one category (i.e. 19 of the 20 children in each group were assessed as having acceptable intubating conditions). One patient in the sevoflurane group had excessive cord movement at laryngoscopy making intubation difficult, while in the halothane group one patient had moderate coughing after intubation. The scores for each category are shown in figure 1. Twelve of 20 children who received halothane had ideal intubating scores of 5 compared with only seven of 20 who received sevoflurane (ns). There was no significant difference between mean total intubation score per patient in the two groups (mean score in the halothane group 5.5; mean score in the sevoflurane group 5.85). There were no significant differences between the groups in assessments of laryngoscopy, coughing, limb movement or jaw relaxation. However, the vocal cords were more likely to be moving or closing in the sevoflurane group (P=0.01). Time to reach the clinical end-point for intubation was reached significantly more rapidly in the halothane group (P=0.015, table 3) and there was no relationship between intubation time and total intubation score (fig. 2).

All patients remained haemodynamically stable during the study with no significant differences between the two groups in HR or MAP before intubation, immediately after intubation, or at 1, 2 or 3 min after intubation. Oxyhaemoglobin saturation remained greater than 95% in all patients throughout the study.

Discussion

Inhalation induction with sevoflurane is undoubtedly a useful addition to the techniques available to the paediatric anaesthetist and has been studied and reviewed extensively.[8–22] Recent studies have noted that induction was more rapid with sevoflurane and halothane when an "overpressure" technique was used rather than using incremental increases in inspired concentration.[12] As part of a meticulous dose-finding study[14] to calculate the ED$_{50}$ and ED$_{95}$ end-tidal sevoflurane concentrations for tracheal intubation, the mean time to reach the ED$_{95}$ value was comparable (213 (SD 23) s) with the times in our study (table 3), despite the fact that the previous study used an overpressure method without nitrous oxide. The overpressure technique has been associ-

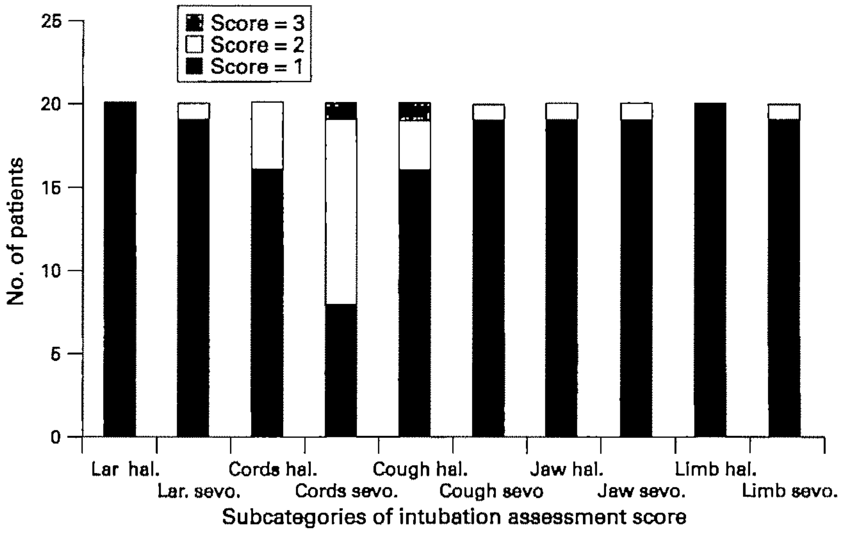

Figure 1 Intubation assessment scores: number of patients with scores of 1, 2 or 3 in each assessment category (laryngoscopy (lar.), vocal cords (cords), cough, jaw relaxation (jaw), limb movement (limb)) for children receiving halothane (hal.) or sevoflurane (sevo.). There were no scores of 4.

Table 3 Time to reach clinical end-point for intubation (pupils small and central) (mean (sd) [range])

	Halothane	Sevoflurane	*P*
Time (s)	200.2 (53.9) [100–277]	243.4 (52.9) [125–335]	0.015

ated with restlessness and agitation during induction, which is improved by adding nitrous oxide.[22] The MAC-reducing properties of 60% nitrous oxide are less for sevoflurane (20–25% *vs* 60% for halothane) which may explain the more rapid induction with incrementally increasing doses of halothane in nitrous oxide, as was seen in our study.

The clinical end-point used in our study was reached in a similar time in a previous study,[21] but sevoflurane-treated children in that study reached the end-point significantly more rapidly (238 (sd 68) s) than halothane-treated patients (290 (sd 87) s) (P=0.027). That study included infants as young as 6 months. Another comparative paediatric study of sevoflurane and halothane included a formal assessment of intubating conditions.[17] In that study, children became apnoeic after approximately 3 min and were not deemed to be ready for intubation until approximately 10 min whether the child received halothane or sevoflurane.[17] Nitrous oxide was used and intubating conditions were assessed using a different, unvalidated scoring system. Although intubating conditions were deemed to be better with halothane, the authors commented that viewing of the vocal cords was difficult in a significant number of patients in both the halothane and sevoflurane groups. Limb movement occurred in 25% of patients in each group. These findings suggest that the induction technique was unsatisfactory in both groups. In our study, we found satisfactory intubating conditions in 38 of 40 patients using the clinical end-point of small centralized pupils. This was achieved within 100–335 s in all cases while maintaining spontaneous ventilation. This end-point was reached significantly earlier with halothane and more ideal intubating conditions were found in children who had received halothane. This may reflect the greater potency of halothane amplified by the larger MAC-reducing effect of nitrous oxide.

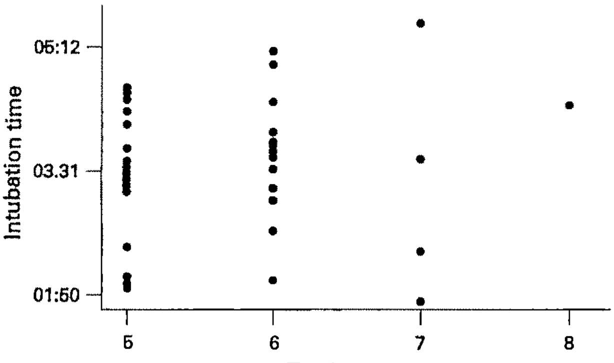

Figure 2 Total intubation scores for each patient *vs* time to reach the clinical end-point for intubation. There was a broad spread of times for each total score.

Although at 1 MAC inspired concentrations, sevoflurane and halothane cause comparable respiratory depression, this has not been confirmed for deep levels of anaesthesia.[20][23] A significant proportion of children attending for adenotonsillectomy have a history of sleep-obstructed breathing and induction time may be longer in this population. The use of a pupillary end-point provides a consistent and reliable clinical sign of readiness for intubation and was achieved in our study relatively quickly. This may be because we used up to 8% sevoflurane or 5% halothane whereas previous studies of time to intubation used lower inspired concentrations.[13][14][22]

In view of the reported high incidence of restlessness with oxygen–sevoflurane mixtures,[22] we felt it was unethical to omit nitrous oxide for elective cases but we recognize that 100% oxygen is needed for induction of anaesthesia in children with airway compromise. Although the results of this study suggest a higher percentage of patients reach ideal intubating conditions more rapidly with incremental halothane than with incremental sevoflurane induction, in all children the trachea was intubated and 38 of 40 children had satisfactory intubating conditions. It is important to formally compare the intubating conditions of sevoflurane–100% oxygen with the gold standard of halothane in oxygen in children with airway compromise.

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British Journal of Anaesthesia 1998; **80**: 456–459

Induction and emergence in infants less than 60 weeks post-conceptual age: comparison of thiopental, halothane, sevoflurane and desflurane

K. O'Brien, D. N. Robinson and N. S. Morton

Summary

We have studied 40 infants with a post-conceptual age of less than 60 weeks undergoing general anaesthesia for herniotomy. Patients were anaesthetized with 1 MAC equivalent values for age and agent and allocated randomly to receive halothane, sevoflurane or thiopental for induction, and halothane, sevoflurane or desflurane for maintenance of anaesthesia. At induction, both time to acceptance of a face mask and loss of eyelash reflex were recorded. Emergence times were noted by a blinded observer. Induction and emergence times were similar between the halothane and sevoflurane groups but were consistently shorter in the desflurane group compared with the halothane or sevoflurane groups. There were no problems at extubation or significant apnoea in any group. Induction of anaesthesia in this population was no quicker with sevoflurane than with halothane and the method used for induction did not influence recovery time. Maintenance of anaesthesia with desflurane resulted in a shorter recovery time in infants in whom anaesthesia was induced with halothane or thiopental. Desflurane maintenance may be particularly beneficial in the neonate. (*Br. J. Anaesth.* 1998; **80**: 456–459)

Keywords: anaesthesia, paediatric; anaesthetics volatile, halothane; anaesthetics volatile, desflurane; anaesthetics volatile, sevoflurane; neonates

Neonates, and especially formerly preterm infants, are susceptible to apnoea and ventilatory depression after general anaesthesia.[1 2] An effect of the residual volatile agent may be responsible. Newer agents, including sevoflurane and desflurane, may have advantages over halothane because of their more rapid recovery characteristics. Sevoflurane has a blood:gas solubility of 0.65 which is intermediate between halothane (2.4) and desflurane (0.45).[3] A lower blood:gas solubility should be associated with a more rapid uptake of the inhalation agent, that is faster induction and more rapid recovery when discontinued. This would suggest that desflurane is a suitable agent for use in paediatric anaesthesia. Unfortunately, its use as an induction agent has been limited by the high incidence of airway irritation during inhalation in paediatric patients.[4] Taylor and Lerman have shown that these complications do not occur at extubation.[5] Sevoflurane provides smooth induction with few side effects and is therefore a suitable agent for use in neonates and infants.[6]

We have compared halothane, sevoflurane and desflurane, as they are used clinically, in infants aged less than 60 weeks post-conceptual age (PCA).

Patients and methods

After obtaining Ethics Committee approval and written informed consent from parents, we studied 40 patients undergoing inguinal hernia repair. Patients were allocated randomly, using a computer-generated randomization table from "Trialaid" (Dr G. Hutchison, Dundee) to one of four groups of 10 patients. Group size was calculated using "Trialaid" on the basis of having a 95% chance of detecting a 40% difference in mean recovery time with a significance value of 0.05 (estimated mean difference in recovery time of 8 min, P=0.05, power=95%, n=10). In group 1, patients received inhalation induction with halothane, and maintenance with halothane throughout the procedure; in group 2, anaesthesia was induced with halothane and maintained with desflurane; in group 3, anaesthesia was induced with i.v. thiopental (STP) and maintained with desflurane; and in group 4, anaesthesia was induced with sevoflurane and maintained with sevoflurane. All infants were fasted and unpremedicated.

All patients had standard monitoring, including electrocardiogram, pulse oximeter and non-invasive arterial pressure, and an i.v. cannula was sited before induction. Anaesthesia was induced using 60% nitrous oxide in oxygen, delivered via a Mapelson F circuit. Initially a cupped hand was placed on the infant's face and then replaced by a mask as tolerated. Stepwise increases of either halothane (0.5% increments) or sevoflurane (1% increments) were made every 5–10 breaths. Atropine was administered only for treatment of bradycardia (heart rate 100 beat min^{-1}). Time to acceptance of a face mask was noted and time to loss of the eyelash reflex was taken as the time to sleep. This was assessed every 10 s. Patients were anaesthetized by one of two senior anaesthetists who were not blinded to the inhalation agent. Fresh gas flow during induction of anaesthesia was 6–8 litre min^{-1} for all infants. If randomized to receive i.v. induction, the infant received thiopental 3–5 mg kg^{-1} as the induction agent. Vecuronium 0.1 mg kg^{-1} was administered to

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Table 1 Post-conceptual age (PCA) at birth, PCA at the time of surgery, weight and total time spent at 1 MAC in infants less than 60 weeks PCA anaesthetized with halothane (Hal.), a combination of halothane induction and desflurane (Des.) maintenance, thiopental (STP) induction and desflurane maintenance, or sevoflurane (Sev.) alone (mean (SD) [range]). There was no significant difference between groups with regard to PCA at birth, at the time of surgery ($P=0.37$, $P=0.93$), or with regard to weight ($P=0.89$) or time spent at 1 MAC ($P=0.98$)

	Group 1 Hal./Hal.	Group 2 Hal./Des.	Group 3 STP/Des.	Group 4 Sev./Sev.
PCA at birth (weeks)	35 (4) [26–40]	36 (4) [27–40]	38 (4) [27–40]	34 (4) [28–40]
PCA at surgery (weeks)	44 (8) [39–60]	46 (4) [42–52]	46 (5) [42–60]	45 (5) [37–56]
Weight	4.1 (1.5)	4.5 (1.0)	4.3 (1.3)	4.5 (1.6)
Time at 1 MAC (min)	39 (11)	40 (13)	39 (9)	38 (11)

Table 2 Time taken to acceptance of a face mask and loss of eyelash reflex in neonates and infants induced with either halothane or sevoflurane (mean (SD)). There was no significant difference between groups with regard to time to face mask acceptance ($P=0.51$) and time to loss of eyelash reflex ($P=0.57$)

	Halothane	Sevoflurane
n	20	10
Face mask acceptance (s)	76 (38)	67 (23)
Loss of eyelash reflex (s)	128 (56)	116 (48)

all infants to facilitate intubation and the lungs were ventilated to normocapnia with 1 MAC of halothane (0.87% neonates, 1.20% infants), desflurane (9.16% neonates, 9.42% infants) or sevoflurane (3.3% neonates, 3.2% infants) according to the randomization.[6 7] When anaesthetized, a caudal block was performed using 0.8 ml kg^{-1} of 0.25% plain bupivacaine (2 mg kg^{-1}) to provide analgesia. Heart rate, non-invasive arterial pressure and rectal temperature were recorded at 5-min intervals throughout the procedure. End-tidal carbon dioxide and end-tidal anaesthetic gas were measured continuously. Haemoglobin oxygen saturation (Sp_{O_2}) was monitored by pulse oximetry. End-tidal inhalation agent was maintained at 1 MAC until surgery was completed and residual neuromuscular block was antagonized with neostigmine 50 μg kg^{-1} and glycopyrrolate 10 μg kg^{-1}.

The infant was then left undisturbed and ventilation continued with 100% oxygen, maintaining normocapnia until spontaneous respiration commenced. The time to first swallow, limb movement (i.e. flexion of the hip joint or movement of the shoulder joint), spontaneous eye opening and extubation were recorded by one of two observers blinded to the agent used. Before the start of the study, both observers were assessed on similar cases to ensure that the same end-points were recorded. Induction, perioperative and immediate postoperative complications were documented. Breath-holding was defined as cessation of breathing or detection of airflow for 10–15 s, and apnoea was defined as cessation of breathing or detection of airflow for 15 s or 15 s with bradycardia (heart rate 80 beat min^{-1}). Coughing, laryngospasm, bronchospasm, excitement and other unanticipated events were recorded. All patients were monitored on the ward using pulse oximetry and chest wall impedance monitoring for 24 h after operation. All charts were reviewed to check for postoperative complications. Patient data, including PCA at birth and at the time of surgery, and weight, were recorded, as was time at 1 MAC.

Statistical analysis was performed using Minitab for Windows version 11.12. Data are reported as mean (SD). Continuous variables were analysed using analysis of variance, with Bonferroni's correction for multiple comparisons. In all cases $P<0.05$ was considered statistically significant.

Results

The groups were comparable in PCA at surgery ($P=0.93$), gestational age at birth ($P=0.37$), weight ($P=0.89$) and time spent at 1 MAC ($P=0.98$) (table 1).

Mean time to acceptance of a face mask was slightly shorter with sevoflurane (67 s) than with halothane (76 s), but this small difference was not statistically significant ($P=0.51$). Similarly, mean time to loss of eyelash reflex was slightly shorter in the sevoflurane group ($P=0.57$) (table 2).

Times from discontinuation of inhalation agent to first swallow, limb movement, eye opening and extubation are shown in table 3. Mean times to limb movement, eye opening (fig. 1) and tracheal extubation were significantly shorter in the two desflurane groups ($P<0.01$) compared with the halothane and sevoflurane groups.

All patients had i.v. cannulae sited before induction of anaesthesia or on the ward if fasting for longer than 4 h. Only one patient required atropine at induction (a very preterm baby who underwent ventilation at birth and was aged 39 weeks (PCA) at the time of surgery). Four patients had an episode of breath-holding during induction, but all were self-limiting. In two of these infants, anaesthesia was

Table 3 Emergence times, including time to first swallow, limb movement, eye opening and extubation in infants less than 60 weeks PCA, anaesthetized with halothane (Hal.), a combination of halothane induction and desflurane (Des.) maintenance, thiopental (STP) induction and desflurane maintenance, or sevoflurane (Sev.) alone (mean (SD)). All times are min:s. $^{**}P<0.01$

	Group 1 Hal./Hal.	Group 2 Hal./Des.	Group 3 STP/Des.	Group 4 Sev./Sev
First swallow	9:04 (4)	7:45 (4)	8:06 (4)	11:04 (3)
Limb movement	12:45 (6)	6:32 (3)**	7:55 (4)**	18:44 (6)
Eye opening	20:36 (8)	11:50 (4)**	11:36 (4)**	20:09 (4)
Extubation	24:09 (8)	14:07 (5)**	14:17 (6)**	20:32 (6)

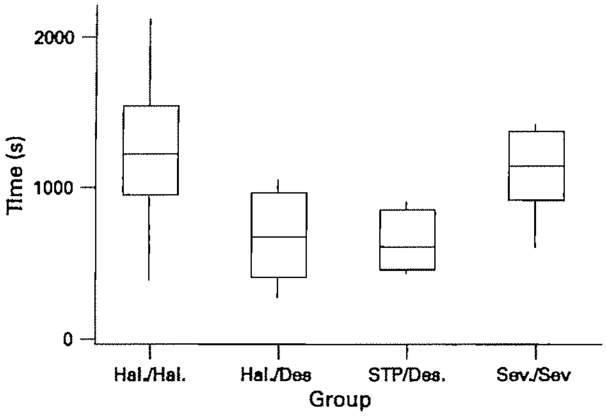

Figure 1 Times to eye opening in the four groups after discontinuation of halothane (Hal.), desflurane (Des.), sevoflurane (Sev.) or thiopental (STP), displayed in boxplot format. The horizontal line across the box=median time; the bottom and top of the box=first and third quartiles; and the vertical line=range of times for each group.

Table 4 Number of patients with respiratory complications, either breath-holding (cessation of breathing for less than 10 s) or apnoea (cessation of breathing for more than 15 s, or for less than 15 s if associated with bradycardia), during induction or recovery in those anaesthetized with halothane (Hal.), a combination of halothane induction and desflurane (Des.) maintenance, thiopental (STP) induction and desflurane maintenance, or sevoflurane (Sev.) alone. There was no clinical difference between groups with regard to respiratory complications at induction or recovery

	Induction		Recovery	
	Apnoea	Breath-holding	Apnoea	Breath-holding
Group 1 Hal./Hal.	0	1	0	2
Group 2 Hal./Des.	0	1	1	0
Group 3 STP/Des.	—	—	0	1
Group 4 Sev./Sev.	0	2	0	1

induced with halothane and both were very premature babies born at 31 and 33 weeks gestational age.

During recovery there was no clinical difference with regard to complications (table 4). In the halothane group there were two episodes of breath-holding, one in a baby with abnormal chest wall movement, and the other in a baby born at 33 weeks with a history of apnoea. There was one episode of breath-holding in the sevoflurane group in a very preterm, low birth weight baby with a history of apnoea. In the desflurane group one baby had an episode of breath-holding, and one baby had two self-limiting apnoeas of 15 s. Both were very premature, low birth weight babies. Two of the babies had complications at induction and recovery. However, as the overall complication rate was low, much larger numbers would be required to show with 95% confidence any significant difference between groups.

Discussion

This study suggests that both halothane and sevoflurane are suitable agents for induction of anaesthesia in neonates and infants. When an overpressure technique is used, both soluble (e.g. halothane) and insoluble (e.g. sevoflurane) drugs provide rapid and similar rates of induction,[8] as confirmed in a recent study.[9] In our study, mean induction times were slightly longer (sevoflurane 1 min 56 s; halothane 2 min 1 s) because of the gradual increase in inspired vapour concentration, but were similar to those of Sarner and colleagues[8] where induction time for sevoflurane (1.6 min) was similar to that for halothane (1.7 min) in a group of older children. The assumption that a MAC multiple of one inhalation agent is equipotent to a similar MAC multiple of another agent may be incorrect.[10] Nitrous oxide decreases the MAC of different volatile agents by varying amounts, having most effect on halothane and least effect on desflurane.[6 11 12] Cardiac output is higher in children and a greater proportion of blood flow is directed to vessel-rich tissues, increasing the concentration of anaesthetic at receptor sites in the brain.[13] The lower solubility of inhalation anaesthetics in blood and tissues of neonates and infants provides an additional explanation for the rapid induction in the halothane group.[14] These factors support our results, showing equally rapid induction in both the halothane and sevoflurane groups.

Respiratory complications occurred in high-risk babies, many of whom had a history of apnoea, in the immediate recovery period. Respiratory complications correlated with patient risk factors and not with the anaesthetic agent.[1 2] We confirmed that airway irritation, which occurs with desflurane at induction, did not cause problems at extubation.[5] Of the 20 patients exposed to desflurane for maintenance of anaesthesia, one exhibited breath-holding and one apnoea after extubation. We studied a high-risk group of patients with 28 of the 40 patients (70%) formerly preterm infants and therefore we might have expected to see more respiratory complications. All patients were monitored in the neonatal surgical ICU for 24 h after operation using both pulse oximetry and chest wall impedance monitors. During that time no child suffered apnoea that required supplementary oxygen or bag and mask ventilation, as assessed by the ward staff. Review of the charts, including nursing notes, revealed absence of any further respiratory complications during this time.

Spinal anaesthesia has been recommended for this patient population because of the increased incidence of apnoea after general anaesthesia[15] but this argument may not hold for the newer, low solubility volatile agents. Our study suggests that recovery from maintenance anaesthesia with desflurane is almost twice as fast as that after halothane or sevoflurane (fig. 1). Recovery times in the two desflurane groups were remarkably similar, suggesting that the method of induction does not influence recovery time but is more dependent on the agent used for maintenance of anaesthesia. Recovery times after halothane and sevoflurane maintenance were similar, which is surprising as maintenance times at 1 MAC were comparable. This could be a result of the confounding effects of nitrous oxide on MAC or of different respiratory depressant effects of the two agents in this patient population. There was no tailoring of MAC levels towards the end of surgery and no external stimulation was allowed to facilitate awakening. The wake-up times shown in table 2 are therefore long. Clinically, time to extubation may be reduced by decreasing vapour concentration towards the end of surgery, thus further decreasing emergence time. For the purposes of this study, all infants had spontaneous eye opening and a regular breathing pattern before extubation. All infants appeared to have clinically effective caudal analgesia, as indicated by the fact that no child required supplementary analgesia for a minimum of 6 h after operation. It is recognized that good regional analgesia may contribute to prolonged awakening. Although desflurane is expensive, requires a special vaporizer and is not suitable for induction because of airway irritant properties, rapid emergence from anaesthesia is possible as a result of its low blood:gas and low tissue:gas solubility.[16] Our results showed that infants receiving desflurane achieved recovery milestones more quickly and were ready for extubation on average 6–10 min before their counterparts receiving other inhalation agents ($P<0.01$). This has particular clinical significance in the neonate.

In summary, the rate of induction and recovery with halothane was comparable with that of sevoflurane in the neonate and formerly preterm infant. However, emergence from anaesthesia was faster in those patients in whom desflurane was used as the maintenance agent, irrespective of the induction agent administered. The incidence of postoperative respiratory complications was low in this study.

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Surgical/tourniquet pain accelerates blood coagulability but not fibrinolysis

S. Kohro, M. Yamakage, J. Arakawa, M. Kotaki, T. Omote and A. Namiki

Summary

Tissue damage during surgery induces coagulation factors and activates platelets. Surgical pain may provoke release of catecholamines, leading to hypercoagulability. We have investigated the effect of surgical pain on blood coagulability and fibrinolysis in orthopaedic operations using tourniquets in 22 patients undergoing total knee replacement. Patients were allocated to one of two groups to receive extradural anaesthesia (EA; n=11) or general anaesthesia (GA; n=11). The EA group received lumbar extradural block with lidocaine. The GA group received only general anaesthesia, maintained with 1.5–2.5% sevoflurane and 66% nitrous oxide in oxygen. Using a thrombelastogram technique, blood coagulability and fibrinolysis were measured. Mean maximum amplitude (MA), which reflects coagulability, increased after tourniquet inflation (11%) in group GA whereas MA in group EA did not change. After tourniquet deflation, MA values in both GA and EA groups increased significantly (10% and 20%, respectively) (P<0.05), and there was also a significant difference in MA between groups (P<0.05). The fibrinolytic rate did not change in either group during tourniquet inflation, but increased significantly (160%) after tourniquet deflation. There was no significant difference in fibrinolytic rate between the groups. We conclude that the hypercoagulability seen in group GA could have been caused by surgical or tourniquet pain, or both, and that extradural anaesthesia is a useful technique to prevent hypercoagulability. (*Br. J. Anaesth.* 1998; **80**: 460–463)

Keywords: blood, coagulation, blood, fibrinolysis, measurement techniques, thrombelastography; pain, surgical; pain, tourniquet

It is known that blood coagulability is exacerbated in the perioperative period.[1–3] Tissue damage during surgery induces coagulation factors and activates platelets at the surgical site.[4] Surgical stress/pain also provokes catecholamine release intravascularly,[5] leading to increased blood coagulability. However, the degree to which these factors affect perioperative coagulability is unclear.

A tourniquet is often used to diminish bleeding during surgery on the lower or upper limbs. Systemic changes in coagulability and fibrinolysis may be affected by surgical pain and also by tourniquet pain because the latter apparently appears 45–60 min after tourniquet inflation under general anaesthesia.[6]

We have investigated the effect of surgical or tourniquet pain, or both, on blood coagulability and fibrinolysis using the thrombelastogram (TEG) and tourniquet techniques, which allow assessment of the coagulability and fibrinolytic process in whole blood samples.[7–9]

Patients and methods

After obtaining approval from the Ethics Committee on Human Research, Sapporo Medical University, and informed consent, we studied 22 patients undergoing total knee replacement using a tourniquet. Patients were excluded if they had abnormalities of blood coagulability or had received medications such as non-steroidal anti-inflammatory drugs. With the exception of small amounts of midazolam (0.05 mg kg^{-1}), no other premedications were used.

Patients were allocated randomly to one of two groups to receive extradural anaesthesia (EA; n=11) or general anaesthesia (GA; n=11). In group EA, an extradural catheter was inserted via the L2–3 or L3–4 interspace. Lidocaine (1.5%) 8–12 ml with epinephrine 1:200 000 were administered through the extradural catheter; smaller doses were then administered, if necessary, to achieve anaesthesia to a level of T5–6. More local anaesthetic was administered as needed to maintain this level of anaesthesia, and patients were sedated with intermittent administration of midazolam 1 mg during surgery. Group GA received only general anaesthesia. Anaesthesia was induced with propofol 3–4 mg kg^{-1}, and a laryngeal mask was inserted. Anaesthesia was maintained with 1.5–2.5% sevoflurane and 66% nitrous oxide in oxygen. Group GA received no i.v. analgesics during surgery.

Whole blood was obtained by antecubital venepuncture before tourniquet inflation, 30 and 90 min after tourniquet inflation, and 5 min after tourniquet deflation. Tourniquet deflation occurred soon after 90 min (table 1). Whole blood (360 μl) was placed in the Thrombelastogram (TEG) C-3000

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Table 1 Patient characteristics and operation data. Values are mean (range). There were no significant differences between the groups for any variable. GA=General anaesthesia, EA=extradural anaesthesia

	Group GA (n=11)	Group EA (n=11)
Sex (F/M)	8/3	8/3
Age (yr)	67 (57–72)	65 (55–76)
Weight (kg)	73 (58–92)	72 (55–89)
Height (cm)	156 (146–172)	152 (140–175)
Heart rate during operation (beat min^{-1})	76 (54–102)	78 (52–95)
Arterial pressure during operation (mm Hg)	118/74 (102–144/54–90)	114/68 (98–154/52–92)
Duration of anaesthesia (min)	171 (137–198)	175 (129–195)
Duration of surgery (min)	111 (97–135)	117 (95–143)
Duration of tourniquet inflation (min)	103 (91–135)	100 (91–125)
Postoperative blood loss (ml)	240 (83–420)	265 (76–580)

(Haemoscope, Glenview, IL, USA) immediately after sampling, and a few drops of mineral oil were spread over the blood surface to prevent evaporation of blood. The TEG records the activity of whole blood coagulation, including cellular and humoral elements, such as interactions of red blood cells, platelets, coagulation factors and calcium.[9] The following variables were measured (fig. 1): reaction time (min); coagulation time (min); maximum amplitude (MA, mm) (which reflects coagulability);[9] and fibrinolytic rate ((MA–A_{60})/MA×100, A_{60}=amplitude 60 min after MA).

Arterial pressure and heart rate were measured every 5 min during anaesthesia and the mean of all measurements calculated. Data are expressed as mean (SD) and comparisons were made using the unpaired, two-tailed t test or one-factor analysis of variance with Fisher's test. In all comparisons, $P<0.05$ was considered significant.

Results

The two groups were comparable in age, sex, weight, height and duration of anaesthesia and surgery, and also in duration of tourniquet inflation (table 1). There were no differences in haemodynamic variables during operation or in the amount of postoperative bleeding for 24 h between the two groups.

Changes in TEG parameters are shown in figure 2. None of the parameters before tourniquet inflation differed significantly between groups EA and GA. Reaction time in group GA was reduced after tourniquet inflation (19%); it did not change during the same period in group EA (fig. 2A). There was a significant difference between groups at 90 min after tourniquet inflation ($P<0.05$). After tourniquet deflation, reaction times increased significantly (20% and 37% in groups EA and GA, respectively) ($P<0.05$). There was no significant difference between groups at this time. Coagulation time in group EA did not change significantly (fig. 2B). In group GA, coagulation time was reduced significantly (39%) after tourniquet deflation ($P<0.05$), and there was a significant difference between groups at this time ($P<0.05$). Similar to the changes in reaction time, maximum amplitude in group GA increased after tourniquet inflation (11%), whereas in group EA it did not change (fig. 2C). After tourniquet deflation, maximum amplitude increased significantly (by 10% and 20% in groups EA and GA, respectively) ($P<0.05$). There were significant differences between groups at 90 min after tourniquet inflation and at 5 min after tourniquet deflation ($P<0.05$). Fibrinolytic rates did not change in both groups during tourniquet inflation (fig. 2D), and after tourniquet deflation, it increased significantly (160%) in both groups ($P<0.05$); there were no significant differences between groups.

Discussion

Using TEG, we have shown that the reaction time in group GA was reduced and maximum amplitude increased, whereas these values did not change in group EA during tourniquet inflation. In general, blood coagulability is accelerated during surgery.[1-3] Surgical trauma increases plasma concentrations of coagulation factors,[3] decreases concentrations of coagulation inhibitors[10] and enhances platelet activity[11] at the site of vascular damage. Simultaneously, surgical pain, including tourniquet pain, provokes the release of catecholamines and serotonin intravascularly, leading to increased blood coagulability.[5] Therefore, the increase in blood coagulability in group GA during tourniquet inflation seemed to depend on surgical/tourniquet pain.

Fibrinolytic rates did not change in both groups during tourniquet inflation. Surgical stress also causes release of plasmin at the site of vascular damage, leading to fibrinolysis.[1] Therefore, we can conclude that surgical or tourniquet pain *per se* had no effect on systemic blood fibrinolysis.

The anaesthetic technique may have an effect on coagulability and fibrinolysis. However, sevoflurane is reported to inhibit blood coagulability *in vivo*,[12]

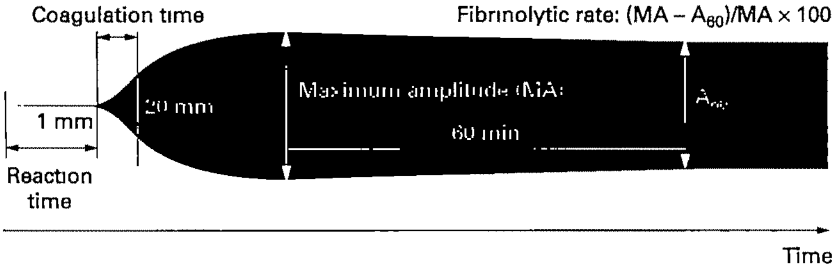

Figure 1 Typical recording of thrombelastogram and measured parameters. Normal ranges: reaction time 7–14 min; coagulation time 3–7 min; maximum amplitude (MA) 40–60 mm; and fibrinolytic rate <10%. Fibrinolytic rate is defined as (MA–A_{60})/MA×100 (A_{60}=amplitude 60 min after MA).

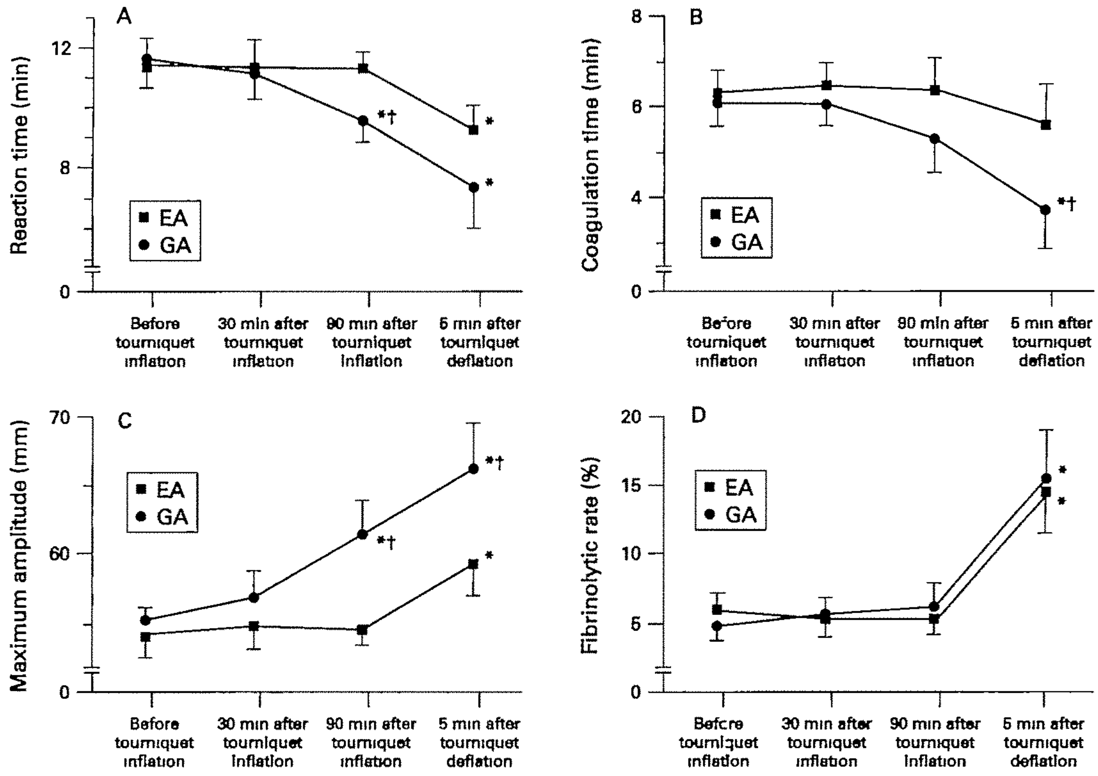

Figure 2 Changes in coagulation–fibrinolysis values measured by thrombelastography during surgery using a tourniquet in the extradural anaesthesia (EA) and general anaesthesia (GA) groups. Data are mean (SD), n=11. *P<0.05 compared with the value before tourniquet inflation; †P<0.05 between groups.

and lidocaine (used in group EA) is reported to have little effect on blood coagulability in clinical doses.[13] Therefore, the difference in anaesthetic techniques is not likely to have had an effect on the differences in blood coagulability and fibrinolysis in this study.

After tourniquet deflation, blood coagulability increased significantly with fibrinolysis in both groups. These changes in blood coagulability–fibrinolysis produced by tourniquet deflation could be caused by release of clotting and anti-clotting factors from the surgical site. However, the degree of blood coagulability in group GA was significantly higher than that in group EA, even after tourniquet deflation. Mean maximum amplitude in group GA was outside the normal range, indicating hypercoagulability. This could be a result of the surgical/tourniquet pain-induced coagulability seen in group GA during tourniquet inflation.

Blood hypercoagulability is thought to lead to thrombotic complications.[2 5 11] Regional anaesthesia has been reported to reduce perioperative morbidity and mortality compared with general anaesthesia.[5] Rosenfeld and colleagues reported that extradural anaesthesia inhibited coagulation and prohibited the development of arterial thrombosis.[14] Our study is the first to demonstrate the role of pain in intraoperative blood coagulability and fibrinolysis under conditions where the regional effects of surgery are excluded.

In summary, surgical/tourniquet pain increased blood coagulability during surgery and this was not accompanied by changes in fibrinolysis. Extradural anaesthesia inhibited the acceleration of blood coagulability compared with general anaesthesia.

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Changes in specific markers of haemostasis during reduction mammoplasty

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Summary

We have investigated the time course of the coagulation and fibrinolytic changes during moderate surgical trauma (elective reduction mammoplasty) in the absence of other confounding factors that could affect haemostasis. Specific markers for coagulation (prothrombin fragment 1.2 (F1.2), thrombin–antithrombin III complex (TAT)) and fibrinolysis (plasmin–antiplasmin complex (PAP) and D-dimer) were examined. Blood samples were obtained in 20 ASA I anaesthetized female patients at T0 (before operation), T75 (during operation) and T150 (before the end of operation). There was a progressive increase in blood loss during operation: mean 110 (SD 80) ml at T75 and 470 (180) ml at T150. This was associated with a significant increase in plasma concentrations of F1.2, PAP and D-dimer at T150 only ($P<0.05$ *vs* T0). We conclude that moderate surgical trauma with blood losses greater than 300 ml can activate thrombin generation and fibrinolysis during operation. (*Br. J. Anaesth.* 1998; **80**: 464–466)

Keywords: blood, coagulation; blood, loss; surgery, haemostatic response; surgery, plastic

Several clinical studies have suggested that the postoperative hypercoagulable state probably begins during operation, reflected by a decrease in antithrombin III, protein C and plasminogen activities,[1–3] and by an increase in thrombin formation.[4–7] In most cases, the intraoperative increase in coagulation activity was observed during extensive surgery, in the presence of haemodilution or blood transfusion, which are known to affect haemostasis.[8–10] In addition, other changes in intraoperative coagulation and fibrinolytic activity have been documented during brain and cardiac procedures, but these tissues can selectively express tissue factor.[11] Finally, these haemostatic changes were found after various operation times, and duration of surgery may influence the postoperative hypercoagulable state.[12] It is not known if moderate surgical trauma and accompanying blood loss could activate intraoperative thrombin generation *per se* without these confounding factors acting on intraoperative haemostasis.

Our aim was to investigate the time course of intraoperative haemostatic response to a surgical procedure with estimated moderate blood loss, in the absence of blood transfusion or haemodilution. We studied patients undergoing reduction mammoplasty because of the homogeneous healthy population, expected moderate intraoperative blood loss[13] and the fact that expression of tissue factor in mammary tissue has not been reported. The intraoperative time course of specific markers for coagulation (prothrombin fragment 1.2 (F1.2) and thrombin–antithrombin III complex (TAT)) and fibrinolysis (plasmin–antiplasmin complex (PAP) and D-dimer) was determined together with assays for factor VIII coagulant activity (VIII:C) and von Willebrand factor antigen (vWF).

Materials and methods

The study was approved by the Hospital Committee for the Protection of Human Subjects. After obtaining informed consent, we studied 26 adult ASA I female patients undergoing elective reduction mammoplasty. Exclusion criteria were recent therapy with salicylates and non-steroidal anti-inflammatory drugs, oral contraceptives, preoperative haemoglobin concentration less than 90 g litre^{-1}, or abnormal blood coagulation by clinical history or by preoperative laboratory screening (platelet count $<100\times10^9$ litre^{-1}, prothrombin time <80%, activated partial thromboplastin time >38 s).

After oral premedication with hydroxyzine 100 mg, anaesthesia was induced with propofol 2.5 mg kg^{-1} i.v. and alfentanil 30 µg kg^{-1} i.v. After administration of atracurium 0.5 mg kg^{-1} i.v. and tracheal intubation, patients underwent mechanical ventilation (tidal volume 10 ml kg^{-1} at 12 bpm) with 65% nitrous oxide in oxygen, maintaining end-expired $P\text{CO}_2$ at 4.0–4.6 kPa. The operating table was adjusted so that the patient was in a semi-sitting position. Anaesthesia was maintained with continuous i.v. infusion of alfentanil 30 µg kg^{-1} h^{-1} and inspired isoflurane at an alveolar concentration required to maintain mean arterial pressure (MAP) at 60–80 mm Hg (Dynamap, Critikon Inc., Tampa, FL, USA). Rectal temperature was maintained at 36–36.5 °C using a heated mattress. Over the whole operation time, patients received Ringer's solution at a rate of 4–6 ml kg^{-1} h^{-1}. If infusion of colloid,

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Table 1 Time course of biological factors in the group of 20 patients (mean (SD)) VIII:C=Factor VIII coagulant activity, vWF=von Willebrand factor antigen, TAT=thrombin–antithrombin III complex, F1.2=prothrombin fragment 1.2, PAP=plasmin–antiplasmin complex. **P*<0.05,***P*<0.01 compared with T0

	T0 min	T75 min	T150 min
Blood loss (ml)	0	110 (80)**	470 (180)**
Haemoglobin (g litre^{-1})	117 (9)	116 (9)	114 (10) *
Packed cell volume (%)	33.6 (2.4)	33.7 (2.3)	32.9 (2.8)
Platelet count (×10^{9} litre^{-1})	240 (43)	250 (47)	242 (49)
Fibrinogen (g litre^{-1})	2.9 (0.7)	2.8 (0.5)	2.6 (0.7)**
VIII:C (%)	81 (24)	80 (30)	77 (22)
vWF (%)	79 (24)	77 (20)	76 (22)
TAT (µg litre^{-1})	3.2 (3.2)	4.2 (4.3)	4.5 (5.2)
F1.2 (nmol litre^{-1})	0.97 (0.40)	1.07 (0.31)	1.25 (0.40)**
PAP (µg litre^{-1})	168 (50)	171 (65)	212 (57)*
D-dimer (µg litre^{-1})	156 (52)	159 (58)	173 (67)**

autologous blood or plasma, or administration of vasoactive drugs were necessary before the study ended, the patient was excluded. Blood loss was determined by weighing sponges and operative drapes. Anatomical specimens were weighed and subjected to histological examination.

The study started in anaesthetized haemodynamically stable patients (T0). Sequential venous blood samples were obtained directly from peripheral foot vein punctures at T0 (before operation), T75 (during operation) and T150 (before the end of operation) while the patient was still anaesthetized in the semi-sitting position. For each period, blood samples were obtained into Vacutainer tubes in the following order: haemoglobin concentration and platelet count into a tube containing 15% sodium EDTA, plasma protein, osmolality and electrolytes into a tube containing lithium heparin (14.3 u. ml^{-1} blood (United States Pharmacopeia units)), and plasma coagulation factors into Diatube H tubes containing CTAD mixture (9:1 vol/vol). All tubes were purchased from Becton Dickinson (Meylan, France). Plasma was separated by centrifugation at 3500 g for 20 min at 18°C, and stored in 250-ml aliquots at −80°C until assayed.

Standard laboratory techniques were used for measurement of osmolality and electrolyte concentration (Hitachi 717, Boehringer Mannheim, Meylan, France). Haemoglobin concentration and platelet counts were measured using a Coulter counter STKS (Coultronics, Margency, France). Chronometric tests were performed on a STA coagulometer (Diagnostica Stago, Asnières, France) for fibrinogen (Fibrinomat, Biomérieux, Marcy-l'Etoile, France; normal range 2–4 g litre^{-1}) and VIII:C (F VIII deficient plasma, Immuno, Orly, France; normal range 70–130%). An enzyme-linked immunosorbent assay (ELISA) was used for measurement of vWF, TAT, F1.2, PAP and D-dimer. TAT complex, F1.2 and PAP concentrations were measured using the Enzygnost TAT micro (normal range 2–4 µg litre^{-1}), Enzygnost F1.2 micro (normal range 0.44–1.11 nmol litre^{-1}) and Enzygnost PAP micro (normal range 99–368 µg litre^{-1}), respectively (Behringwerke AG, Marburg, Germany). vWF and D-dimer were measured using the Asserachrom vWF (normal range 60–130%) and Asserachrom D-dimer (normal value less than 400 µg litre^{-1}), respectively (Diagnostica Stago, Asnières, France). All samples were assayed in duplicate and performed in parallel, with standard curves generated from titrated plasma.

STATISTICAL ANALYSIS

Results are expressed as mean (SD). Analysis of the data was performed using one-way analysis of variance (ANOVA) for repeated measurements (StatView SE program, Abacus Concepts Inc., Berkeley, CA). Each value was compared with that obtained at control (T0) using the Scheffé *F* test, with a significance level of 0.05.

Results

Of the 26 patients enrolled in the investigation, six did not complete the study because of technical problems in blood sampling in five, and requirement for autologous blood transfusion in one patient. The study population consisted of 20 female patients, mean age 28 (range 19–49) yr and mean weight 62 (SD 9) kg. Mean operation time was 200 (50) min. The anatomic specimens weighed 830 (380) g (range 260–1760 g), and showed no signs of malignancy on histological examination.

There was progressive intraoperative blood loss, resulting in a small decrease in haemoglobin concentration at T150 while packed cell volume remained unchanged (table 1). At T75, there was no significant change in the plasma values of the haemostatic variables. However, at T150 the plasma concentration of fibrinogen decreased significantly (*P*<0.01), while plasma concentrations of F1.2, PAP and D-dimer increased significantly (*P*<0.05). These haemostatic changes corresponded to a mean increase of 34% for F1.2, 25% for PAP and 10% for D-dimer from their values at T0. There were no changes in platelet count or plasma VIII:C and vWF concentrations. There was no significant change in the values of plasma sodium and osmolality throughout the study (data not shown). No patient had clinical evidence of deep vein thrombosis in the postoperative period.

Discussion

Thrombin formation is a key regulatory step in haemostasis. Trace plasma proteins, activated on exposure to tissue factor, initiate a series of reactions culminating in the conversion of prothrombin to thrombin.[14] During this process, the amino terminal of the prothrombin molecule is cleaved to generate the inactive F1.2 fragment. The short half-life of active thrombin, primarily caused by the inhibitory effect of antithrombin III, precludes direct measurement of plasma thrombin concentration. Therefore, the F1.2 assay provides a direct immunochemical measurement of prothrombin activation and thrombin generation *in vivo*. As the selective cellular expression of tissue factor in humans is restricted to the perivascular cells,[11] activation of blood coagulation via contact of tissue factor with blood during surgical trauma is expected. However, no such change has been found in plasma TAT concentrations, mainly because of intra-individual variability of TAT measurements. F1.2 is then a sensitive marker of prothrombin activation, as noted previously in patients anticoagulated with warfarin.[15]

Intraoperative thrombin generation was associated with increased fibrinolytic activity, indicated by an increase in plasma values of PAP and D-dimer at T150. When plasmin acts on cross-linked fibrin, E fragments and D-dimers are generated. Through the serine of its activation site, plasmin bonds with α_2 plasmin inhibitor to form PAP complex. Therefore, PAP is a direct indicator of plasmin activity, while D-dimers reflect degradation of fibrin. Increased plasma concentrations of PAP and D-dimers have been reported after trauma[16] and during major orthopaedic surgery.[6] Fibrinolysis is activated mainly by tissue plasminogen activator (tPA). Although concentrations of tPA were not measured in this study, mammary tissue is not known to contain high concentrations of tPA. However, thrombin is one of the stimuli for secretion of tPA by the endothelial cells.[17] This suggests that enhanced fibrinolysis was secondary to thrombin generation in our study.

Although we did not measure plasma concentrations of catecholamines, intraoperative plasma values of vWF and VIII:C, which may be related to the endocrine response to anaesthesia,[18] remained unchanged. Thus prothrombin activation was related to surgical trauma during non-stress anaesthetic conditions.

We have isolated surgical trauma and accompanying blood loss (>300 ml) as determinants of intraoperative activation of thrombin generation and fibrinolysis, in the absence of confounding factors acting on intraoperative haemostasis. However, these haemostatic changes are small compared with those observed during major surgical procedures where F1.2 concentrations were >3 nmol litre^{-1}.[5 6] In both studies, the highest concentrations of F1.2 were observed in the postoperative period. Conversely, no significant intraoperative change in F1.2 was found during elective craniotomy with blood losses <250 ml.[7] No change in haemostatic response was found during ophthalmic surgery whatever the anaesthetic technique.[19] This indicates that associated factors such as blood transfusion or major blood losses could have a prominent role in intraoperative activation of coagulation.

Increased plasma concentrations of TAT, F1.2 and D-dimer have been found to correlate with thrombotic tendency.[15 20] The moderate changes in these markers in our study make it difficult to translate these results into a real risk of venous thromboembolism or recommend a form of prophylaxis for this type of surgical procedure. Postoperative assessment of these specific markers of haemostasis coupled with limb venography would be needed to establish guidance. Nevertheless, this study confirmed that activation of thrombin generation begins during operation, even during moderate surgical trauma.

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British Journal of Anaesthesia 1998; **80**: 467–469

Effect of remifentanil on the haemodynamic response to orotracheal intubation

J. P. THOMPSON, A. P. HALL, J. RUSSELL, B. CAGNEY AND D. J. ROWBOTHAM

Summary

We have examined the effect of remifentanil on the haemodynamic response to orotracheal intubation in a randomized, double-blind study. We studied 40 patients allocated to one of four groups of 10 each, to receive the following immediately before induction of anaesthesia: remifentanil 1 μg kg^{-1} bolus over 30 s, followed by an infusion of 0.5 μg kg^{-1} min^{-1}; saline placebo only; glycopyrrolate 200 μg and remifentanil 1 μg kg^{-1} bolus over 30 s, followed by an infusion of 0.5 μg kg^{-1} min^{-1}; or glycopyrrolate 200 μg only. Anaesthesia was induced with propofol, vecuronium and 1% isoflurane with 66% nitrous oxide in oxygen. The trachea was intubated under direct laryngoscopy 3 min after induction of anaesthesia. Arterial pressure and heart rate were measured non-invasively, immediately before induction of anaesthesia and then at 1-min intervals. Remifentanil was found to effectively attenuate the pressor response to intubation ($P<0.05$ for the increase in mean arterial pressure; $P<0.01$ for the increase in heart rate). In the absence of a concurrent vagolytic agent, remifentanil was associated with bradycardia or hypotension, or both, in five of 10 patients, compared with one patient who received remifentanil and glycopyrrolate. (*Br. J. Anaesth.* 1998; **80**: 467–469)

Keywords: analgesics opioid, remifentanil; premedication, glycopyrrolate; intubation tracheal; intubation tracheal, responses; cardiovascular system, effects

The pressor response to tracheal intubation, resulting in tachycardia and hypertension, is well described.[1] Plasma concentrations of catecholamine are increased[2 3] and there may be associated myocardial ischaemia.[4] Haemodynamic responses may be attenuated by several methods, including administration of i.v. opioids,[5] vasodilators,[6] β-blockers[7] or by deepening of anaesthesia. Remifentanil is a new opioid agent that is structurally unique. An ester bond renders it subject to rapid hydrolysis by non-specific blood and tissue esterases and thus it has a short half-life.[8] Speed of onset of effect is rapid (1–2 min) and similar to that of alfentanil.[9] Therefore, remifentanil may be appropriate for attenuation of the pressor responses to brief but noxious stimuli. The aim of this study was to assess the effect of remifentanil on changes in heart rate and arterial pressure after intubation. In view of the reported association of remifentanil with bradycardia,[10] the effect of concurrent administration of glycopyrrolate was also examined.

Patients and methods

After obtaining approval from the local Research Ethics Committee and informed written consent, we studied 40 ASA I–II female patients, aged 18–48 yr, presenting for elective surgery. Patients were assigned to one of four treatment groups of 10 patients each, to receive the following in a randomized, double-blind manner: remifentanil 1 μg kg^{-1} bolus given over 30 s, followed by an infusion of 0.5 μg kg^{-1} min^{-1}; saline placebo only; glycopyrrolate 200 μg and remifentanil 1 μg kg^{-1} bolus given over 30 s, followed by an infusion of 0.5 μg kg^{-1} min^{-1}; and glycopyrrolate 200 μg only. All treatments were given immediately before induction of anaesthesia. Anaesthesia was induced with a bolus dose of propofol 0.5 mg kg^{-1} followed by 10 mg every 10 s titrated to loss of verbal contact, vecuronium 0.1 mg kg^{-1}, and 1% isoflurane with 66% nitrous oxide in oxygen. We ventilated the patients' lungs manually using a Bain system for 3 min after which the trachea was intubated under direct laryngoscopy. Thereafter the lungs were ventilated mechanically using a Manley ventilator (tidal volume 10 ml kg^{-1}, target end-tidal carbon dioxide partial pressure 4.0–4.5 kPa: Datex Capnomac). Arterial pressure was measured non-invasively using an automatic oscillometric device (Datex Cardiocap), and heart rate recorded from the ECG trace. Observations of heart rate (HR), systolic arterial pressure (SAP), mean arterial pressure (MAP) and diastolic arterial pressure (DAP) were recorded every minute from the start of induction to 5 min after intubation (nine time points). Hypotension (SAP <80 mm Hg for >60 s) was treated with ephedrine 3-mg or atropine 300-μg increments i.v. (HR <50 beat min^{-1}); bradycardia (heart rate <45 beat min^{-1} for >60 s) was treated with atropine 300-μg increments i.v.

Statistical analysis was performed using two-way and multivariate analysis of variance for repeated measures (ANOVA, MANOVA with treatment group and time as the between- and within-group factors) and paired and unpaired *t* tests with Bonferroni post-test analysis, as appropriate, using SPSS for Windows computer software (release 6.0., 1993).

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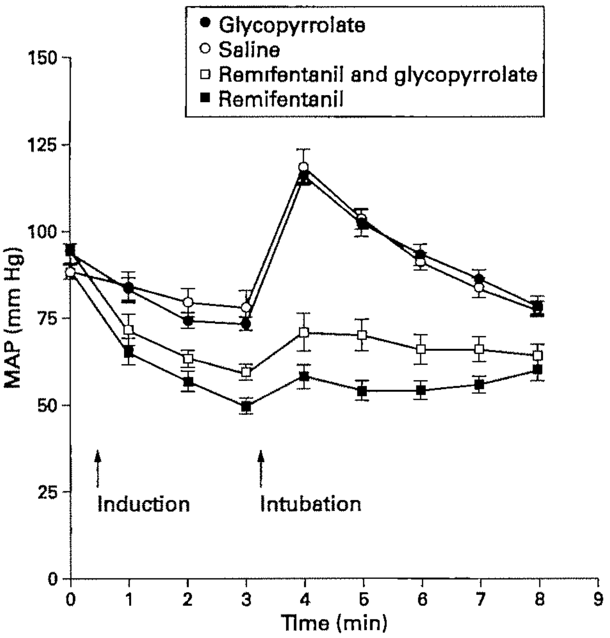

Figure 1 Mean (SEM) mean arterial pressure (MAP) in the glycopyrrolate, saline, remifentanil–glycopyrrolate and remifentanil groups. Preinduction MAP is represented by t=0; induction and intubation are indicated by arrows.

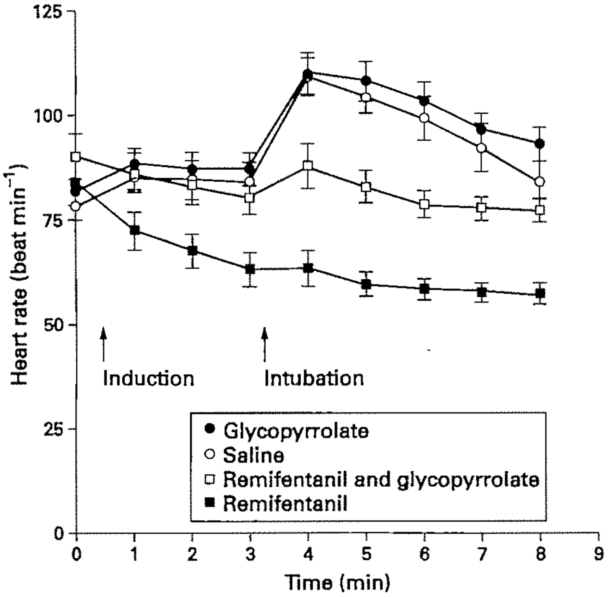

Figure 2 Mean (SEM) heart rate in the glycopyrrolate, saline, remifentanil–glycopyrrolate and remifentanil groups. Preinduction HR is represented by t=0; induction and intubation are indicated by arrows.

Results

Patient characteristics were similar in all four groups. Patients who received remifentanil required less propofol to produce loss of consciousness than those in the non-remifentanil groups (mean 1.66 (SEM 0.12) mg kg^{-1} *vs* 2.23 (0.17) mg kg^{-1}; P=0.01). MAP and HR over the nine times are shown in figures 1 and 2, respectively. SAP and DAP changed in parallel with MAP and therefore have not been reported. There were no differences in MAP or HR before induction of anaesthesia between the groups.

MAP and HR decreased in all groups after induction of anaesthesia (P<0.01). MAP was lower in the remifentanil groups than in the non-remifentanil groups 1 min before intubation (P<0.01). MAP increased significantly in all groups after laryngoscopy and tracheal intubation (P<0.01) but was significantly greater in the non-remifentanil groups than in the remifentanil groups (P<0.05). Mean increases in MAP at intubation were 39.9 mm Hg, 42.0 mm Hg, 8.1 mm Hg and 11.3 mm Hg in the saline, saline–glycopyrrolate, remifentanil and remifentanil–glycopyrrolate groups, respectively; MAP remained below pre-induction values in the remifentanil groups. There were no significant differences in MAP between the remifentanil and remifentanil–glycopyrrolate groups and the saline and glycopyrrolate groups before and after tracheal intubation.

HR decreased in all groups after induction of anaesthesia (P<0.01), and was significantly lower in the remifentanil group immediately before intubation compared with the three other groups (P<0.01) and compared with pre-induction values (P<0.001). HR increased after intubation in the non-remifentanil groups (P<0.001) and was significantly greater 1 min after intubation in the non-remifentanil groups compared with the remifentanil groups (P<0.01). There were no significant differences in HR immediately before and after intubation in the remifentanil and remifentanil–glycopyrrolate groups.

Five patients in the remifentanil group and one in the remifentanil–glycopyrrolate group had bradycardia (HR <45 beat min^{-1}) or hypotension (SAP <80 mm Hg), or both, requiring rescue medication.

Discussion

We have found that a bolus dose of remifentanil 1 μg kg^{-1} given over 30 s, followed by an infusion of 0.5 μg kg^{-1} min^{-1} at induction of anaesthesia, attenuated the haemodynamic responses to orotracheal intubation. MAP decreased in all four groups after induction of anaesthesia. This decrease was greatest in the remifentanil group and was associated with bradycardia. Glycopyrrolate 200 μg given immediately before remifentanil produced no increase in heart rate but attenuated the bradycardia caused by remifentanil. The decrease in MAP after induction of anaesthesia was less in the remifentanil–glycopyrrolate group, although this was not statistically significant. However, clinically relevant hypotension requiring rescue medication was required in five of the remifentanil patients, but in only one patient in the remifentanil–glycopyrrolate group. Intubation had no significant effect on HR in the remifentanil or remifentanil–glycopyrrolate groups. MAP increased significantly in all four groups, but in the remifentanil groups this increase was quantitatively less and did not exceed baseline preinduction values.

Other workers have reported hypotension and bradycardia associated with remifentanil using similar regimens. Schüttler and colleagues, in a large multicentre study, compared remifentanil with alfentanil using an induction drug combination and dosage similar to ours for their remifentanil group.[11] However, all patients received either atropine or glycopyrrolate and prehydration with a crystalloid solution (5 ml kg^{-1}) before induction of anaesthesia. They reported that 53% of patients had a significant hypotensive episode during operation and 4% had a significant bradycardia. However, patients were undergoing major abdominal surgery and no distinction was made in respect of timing of the episode or whether or not the aetiology was in fact surgical or drug-related.

Two multicentre studies have reported on the use of remifentanil as part of a total i.v. anaesthesia regimen.[12,13] Both studies used prehydration with a crystalloid solution but a vagolytic agent was not given. Hogue and colleagues[12] reported an incidence of hypotension on induction of anaesthesia of 10% with a dose of remifentanil identical to that used in our study. In a second group who received a higher infusion rate of 1 $\mu g\ kg^{-1}\ min^{-1}$, the incidence of hypotension was 15% although this difference was not found to be statistically significant. Bradycardia occurred in 7% and 19% of patients, respectively, but this difference was not significant. Philip and colleagues[13] also used a remifentanil bolus dose of 1 $\mu g\ kg^{-1}$ and an infusion of 0.5 $\mu g\ kg^{-1}\ min^{-1}$ after induction of anaesthesia with propofol 2 $mg\ kg^{-1}$. In patients undergoing gynaecological laparoscopic surgery, they reported a 17% incidence of hypotension/bradycardia throughout the operative period, but no distinction was made between the induction and intubation phases. It is possible that prehydration or the absence of a volatile anaesthetic agent, or both, are protective against the development of bradycardia and hypotension.

The size of the pressor response observed in those patients who did not receive remifentanil in our study was similar to that reported previously.[1–7] All patients in this study were healthy, of ASA grade I-II, and in the absence of data relating to the effect of remifentanil in this setting, the inclusion of these control groups was felt to be justified. We appreciate that this approach would be inappropriate in patients at risk of myocardial ischaemia,[7] particularly as the effect of remifentanil has now been quantified.

In our study 50% of patients who received remifentanil without glycopyrrolate exhibited hypotension and bradycardia that required rescue medication. One of the patients in the glycopyrrolate–remifentanil group was similarly affected; mean MAP in this group reached a nadir of 59 mm Hg immediately before intubation.

In summary, these results suggest that remifentanil attenuated the haemodynamic response to laryngoscopy and orotracheal intubation but pretreatment with a vagolytic agent may be required if the incidence of bradycardia and hypotension is to be minimized. It is possible that a lower dose of remifentanil may be effective while producing less hypotension, and further studies are required to investigate the optimal regimen.

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Appropriate size and inflation of the laryngeal mask airway

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Summary

We have compared size 3 and size 4 laryngeal masks in 30 females and size 4 and size 5 in 30 males for success rate of insertion, incidence of airleak and pressure exerted on the pharynx. First, the *ex vivo* volume–pressure relationship of the mask was obtained. Second, after insertion of a mask, the cuff was inflated with the recommended maximum volume of air and intracuff pressure measured. Third, the incidence of airleak during a steady airway pressure of 18 cm H_2O was noted. Fourth, the cuff was deflated until it just prevented airleak, and cuff pressure was measured. The mask was removed, the other size was inserted and the same procedure repeated. At the end of operation, final *in vivo* and *ex vivo* pressures were measured. The pressure exerted on the pharynx was calculated as the difference between *ex vivo* and *in vivo* intracuff pressures. It was always possible to insert both sizes in both sexes. In females, airleak occurred in 15 patients with the size 3 and in five patients with the size 4 (difference: P=0.005) and in males, 21 patients with the size 4 and in four patients with the size 5 (P<0.001). Removal of air to the minimum effective volume significantly decreased intracuff pressure and pressure on the pharynx; on removal of the mask, pressures were similar to, or lower than, initial pressures. Therefore, a larger mask (size 4 in females and size 5 in males) provided a better seal than a smaller size without producing higher pressures on the pharynx. (*Br. J. Anaesth.* 1998; **80**: 470–474)

Keywords: equipment, masks anaesthesia; intubation tracheal

The instruction manual of the laryngeal mask indicates that size 4 should be used in adults of average or large size, and size 3 in children or small adults of more than 25 kg in weight.[1] After introduction of a larger size (size 5), the inventor recommended using as large a size of mask as possible.[2] Despite these instructions, the size 3 laryngeal mask seems to be used frequently in females and the size 4 in males,[3] although larger masks have been used increasingly in controlled studies.[4 5] However, there has been only one study in which an attempt was made to determine the appropriate size of the laryngeal mask.[6]

One method of studying this is to compare the incidence of airleak from the gap between the mask and pharynx for different sizes of masks during positive pressure ventilation. The size of mask which is associated with a lower incidence of airleak may be appropriate. Another method is to identify which size of mask exerts the lowest pressure on the pharynx. When the pressure exerted by the mask on the pharynx is greater than mucosal capillary perfusion pressure, there is a theoretical possibility of mucosal ischaemia. There have been reports of temporary paralysis of the hypoglossal nerve after anaesthesia in patients in whom a laryngeal mask had been used, and high pressure exerted by the mask on the nerve has been considered to be one possible cause.[7 8] This problem may be minimized when the cuff is inflated with the minimum volume of air that effectively prevents airleak around the mask.

The pressure exerted on the pharynx is not known when the cuff is inflated with the minimum effective volume of air, nor is the time course of the change in pressure during anaesthesia. Furthermore, it is not known if masks of different sizes produce different pressures on the pharynx.

We investigated if there were any differences between two sizes of the laryngeal mask (sizes 3 and 4 in females and sizes 4 and 5 in males) in the success rate of insertion, incidence of airleak during positive pressure ventilation and pressure exerted on the pharynx by the mask which was inflated with the minimum effective volume of air.

Patients and methods

After obtaining approval from the local Research Ethics Committee and written informed consent, we studied 30 males and 30 females (ASA I or II, aged 18–80 yr) undergoing elective surgery in whom the use of a laryngeal mask was indicated. Patients with any pathology of the neck, upper respiratory or upper alimentary tract, or at risk of pulmonary aspiration of gastric contents were excluded. Patients with Mallampati class 3[9] or class 4[10] were also excluded.

PRESSURE MONITOR DEVICE

Intracuff pressure was measured using a portable, electrically powered pressure transducer with a built-in amplifier and digital display.[11] This monitor

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was built by, and had been checked by, the Department of Physics, University of Wales College of Medicine. The transducer has a low compliance with a small internal volume (150 µl) which allows measurement of pressure within an inflated cuff by connecting the cuff pilot tube directly to the transducer. The transducer response is linear over the range −50 to +300 mm Hg, and a built-in reference voltage allows calibration. The monitor was calibrated before each measurement.

EX VIVO VOLUME–PRESSURE RELATIONSHIP

Before placement of the laryngeal mask, the pressure–volume relationship was obtained. A three-way tap was connected to the laryngeal mask and the electronic pressure transducer was connected to the second port of the tap. The three-way tap was opened to air so that intracuff pressure was at atmospheric pressure. A 50-ml syringe was connected to the third port and the cuff was deflated by the method described in the manufacturer's instruction manual[1 2] until intracuff pressure reached an arbitrarily defined initial pressure of 20 mm Hg below zero.

The initial volume of air in the syringe was set at 20, 30 and 40 ml, for sizes 3, 4 and 5 laryngeal masks, respectively. The device was held in air, the cuff was gradually inflated and the pressure–volume relationship obtained. The cuff was deflated again to the optimal shape and the pressure was adjusted to 20 mm Hg below zero.

EFFECTIVE MINIMUM VOLUME AND PRESSURE

After preoxygenation of the patient, anaesthesia was induced with a sleep dose of propofol 2.5–3.0 mg kg^{-1} i.v., supplemented with fentanyl 1 µg kg^{-1}. Anaesthesia was maintained with an adequate concentration of either enflurane or isoflurane in oxygen until the patient was transferred to the operating theatre.

In a randomized, cross-over design, sizes 4 and 5 masks were used in males and sizes 3 and 4 in females. The order was randomized by tossing a coin. The laryngeal masks were inserted using the technique described in the manufacturer's instruction manual.[1 2] The cuff of the mask was inflated initially with the recommended maximum volume of air (20 ml for size 3, 30 ml for size 4 and 40 ml for size 5).[1 2] Intracuff pressure was measured. An assistant held the tube of the laryngeal mask to prevent dislodgement and then the laryngeal mask was connected to a Mapleson D breathing system. Adequacy of ventilation was assessed. Ventilation was judged to be adequate when the chest expanded satisfactorily with a clinically acceptable force applied to the reservoir bag during inflation. If it was not possible to ventilate the lungs adequately, one more attempt at placement of the laryngeal mask was allowed. If unsuccessful, the study was abandoned and the airway was maintained either via a face mask or tracheal tube.

After confirmation of adequacy of ventilation, airway pressure was maintained at an arbitrarily determined pressure of 18 cm H_2O by squeezing the reservoir bag for 10 s. Inflation pressure was measured using an airway pressure gauge. The incidence of airleak around the mask was recorded. When there was no leak, air was withdrawn gradually from the cuff until an audible leak occurred around the mask. One millilitre of air was reinserted into the cuff and the volume of air aspirated into the syringe and intracuff pressure were recorded. The volume of air remaining in the laryngeal mask and pressure at this point were considered as the minimum effective volume and pressure. The mask was removed, a laryngeal mask of the other size was inserted and the procedure repeated.

MAINTENANCE OF ANAESTHESIA

The second laryngeal mask was left in place. A bite block (a wad of gauze) was inserted and the laryngeal mask and bite block were fixed to the patient's face with tape.[1 2] The patient was transferred to the operating theatre and nitrous oxide was added to the general anaesthetic. Anaesthesia was maintained with a volatile agent and 66% nitrous oxide in oxygen, with the patient breathing spontaneously.

Intracuff pressure was recorded every 5 min during surgery; immediately before removal of the mask, final intracuff pressure was measured. The mask was removed under deep anaesthesia and the volume of gas in the cuff was measured. After removal of the mask, nitrous oxide and the volatile agent were discontinued, and 100% oxygen was given. The patient's airway was maintained using a face mask.

EX VIVO INTRACUFF PRESSURE AFTER REMOVAL

Immediately after removal of the mask, the cuff was re-inflated with the same volume of gas withdrawn from the cuff before removal, and *ex vivo* intracuff pressure was recorded.

STATISTICAL ANALYSIS

The number of attempts at insertion of the laryngeal mask, presence of airleak around the mask, presence of dislodgement of the mask and incidence of airway obstruction or apparent pulmonary aspiration were recorded.

The pressure exerted by the mask on the tissues (pharyngeal mucosal pressure) was calculated by the difference between intracuff pressure measured with the mask in place ($P_{in\ vivo}$) and that with the mask held in air ($P_{ex\ vivo}$), with the cuff inflated with the same volume of gas.

$$P=P_{in\ vivo}-P_{ex\ vivo}$$

where the same volume of gas was inserted into the mask. The chi-square test was used to compare the incidence of airleak between sizes 3 and 4 masks in females and sizes 4 and 5 masks in males.

Normal plots (plots of normal scores) and the Shapiro–Francia W' test showed that some data for the pressure exerted on the pharynx were not normally distributed, even if the data were transformed. Therefore, Friedman's non-parametric two-way analysis of variance was used to compare the difference in the pressure exerted on the pharynx at the following three times: initial maximum inflation, effective minimum inflation and on removal of the mask. If this was significant, the Wilcoxon matched pairs signed rank sum test was used to compare pressures at initial maximum inflation and at the effective

Table 1 Volume of gas in the cuff of the laryngeal mask at maximum inflation, minimum volume of gas in the cuff which just prevented airleak (effective minimum volume) and volume of gas on removal of the mask (median [approximate 95% confidence limits] (range)). [a]Number of patients in whom the effective minimum volume was measured; [b]number of patients in whom the volume on removal was measured. The numbers of male patients differed for size 4 and 5, as the size of the mask which was used during anaesthesia was determined by tossing a coin (see text for details)

	Maximum volume	Effective minimum volume	Volume at removal
Females			
Size 3 (*n*=30[a], 15[b])	20	18 [15, 20] (3–20)	21 [17, 22] (9–23)
Size 4 (*n*=30[a], 15[b])	30	24 [17, 27] (5–30)	29 [17, 33] (17–33)
Males			
Size 4 (*n*=30[a], 17[b])	30	30 [30, 30] (2–30)	34 [32, 35] (18–36)
Size 5 (*n*=30[a], 13[b])	40	27 [22, 31] (5–40)	30 [20,36] (17–52)

minimum inflation, and those at initial maximum inflation and on removal of the mask. *P* values were adjusted for ties. $P<0.05$ was considered significant.

Confidence limits for the median for each value were calculated using the SINTERVAL command (sign test) in Minitab release 8.2, which shows a confidence level close to 95%. Confidence limits for the median difference were calculated for the difference between the pressures at initial maximum inflation and at the effective minimum inflation, and the pressures at initial maximum inflation and on removal of the mask. This was performed using a method described by Gardner and Altman[12] ; the WINTERVAL command (Wilcoxon confidence limits) in Minitab release 8.2 was used for this calculation, which shows a confidence level close to 95%.

From a preliminary study of approximately 50 patients of each sex, the incidence of airleak was approximately 60% when the smaller size of laryngeal mask was used (size 3 in females and size 4 in males) whereas the incidence was less than 20% when the larger size was used. To detect this reduction with a power of 90% and $P=0.05$, approximately 30 patients of each sex were required.[13] Therefore, we studied 30 females, aged 22–74 yr, weight 46–91 kg (mean 68 kg), and 30 males, aged 20–73 yr, weight 62–110 kg (mean 80 kg).

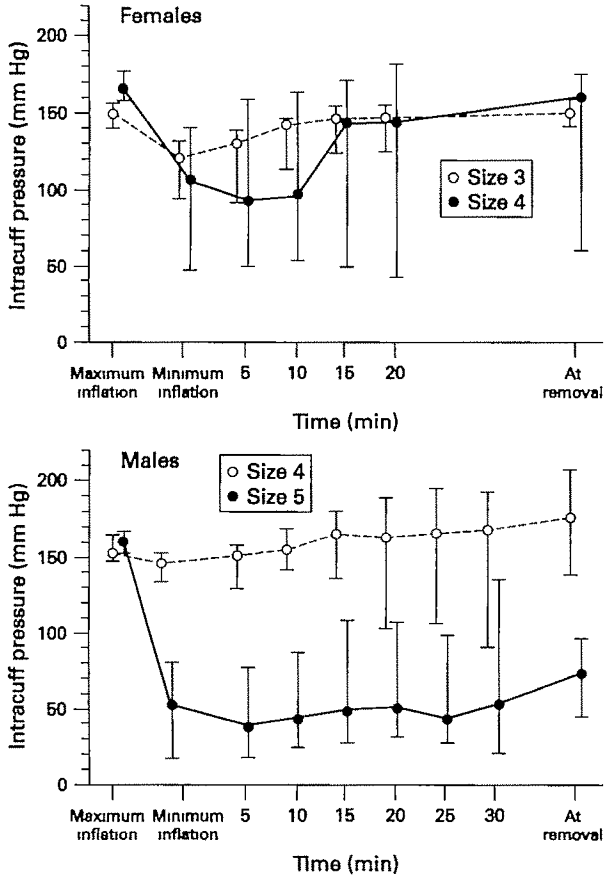

Figure 1 Intracuff pressure *vs* time for size 3 and size 4 laryngeal masks in females, and for size 4 and size 5 in males at the times indicated. Values are median (approximate 95% confidence intervals for medians).

Results

All masks were inserted at the first attempt and a patent airway was obtained in all patients. There were no dislodgements of the mask, airway obstructions or pulmonary aspiration during anaesthesia. Durations of use of the laryngeal mask were similar between the two sizes in both sexes: mean time in females 30 (range 15–55) min and 27 (15–45) min for sizes 3 and 4, respectively; in males 50 (15–90) min and 45 (15–90) min for sizes 4 and 5, respectively.

AIRLEAK AROUND THE MASK

After insertion of the laryngeal mask, the incidence of airleak around the mask was examined while airway pressure was maintained at 18 cm H_2O. In females, air leaked in 15 of 30 patients (50%) when a size 3 mask was used, whereas it occurred in only five patients (17%) with size 4. In males, the incidence was 21 in 30 patients (70%) with the size 4 and four patients (13%) with size 5. The incidence of airleak was significantly lower when a larger mask was used in females ($P=0.005$) and males ($P<0.001$).

CUFF VOLUME

When no airleak occurred, air was withdrawn from the cuff until the minimum effective volume was reached. In females, the minimum effective cuff volume was 3–20 ml for size 3 and 5–30 ml for size 4; in males, values were 2–30 ml for size 4 and 5–40 ml for size 5 (table 1).

Median cuff volumes at removal of the mask were greater than median minimum effective cuff volumes; however, they were still lower than the initial maximum volumes when a larger mask (size 4 in females and size 5 in males) was used (table 1).

INTRACUFF PRESSURE

When the mask was inflated initially with the maximum volume of air, intracuff pressure exceeded 100 mm Hg in both sexes, regardless of the size of the

Table 2 Median intracuff pressure of the laryngeal mask and median pressure exerted by the cuff on the pharynx, at initial maximum inflation, at the minimum effective inflation and on removal of the mask. Friedman's two-way analysis of variance showed that the pressures exerted on the pharynx were significantly different for the three times; P values were calculated using Wilcoxon matched pairs signed rank sum test for the difference between pressures at initial maximum inflation and at the effective minimum inflation, and the difference between pressures at initial maximum inflation and on removal. The approximate 95% confidence limits (CL) for medians were calculated using sign test and confidence limits for median difference using the Wilcoxon confidence limit. The numbers of male patients differed for sizes 4 and 5, as the size of the mask which was used during anaesthesia was determined by tossing a coin (see text for details)

		At minimum effective volume			At removal		
	At maximum volume (control value) (mm Hg)	Pressure (mm Hg)	Difference from control CL	P	Pressure (mm Hg)	Difference from control CL	P
Intracuff pressure							
Females							
Size 3 (n=15)	149.5	121.0	[−67.5, −17.0]	—	150.0	[−34.0, 18.0]	—
Size 4 (n=15)	165.5	107.0	[−97.0, −47.0]	—	160.5	[−80.0, 4.5]	—
Males							
Size 4 (n=17)	152.5	146.0	[−60.0, 0.0]	—	176.0	[−17.0, 41.5]	—
Size 5 (n=13)	160.5	53.5	[−125.0, −75.0]	—	74.0	[−110.0, −45.0]	—
Pressure on the pharynx							
Females							
Size 3 (n=15)	42.0	37.0	[−13.0, 2.0]	0.30	32.0	[−13.5, 5.5]	0.17
Size 4 (n=15)	50.0	38.0	[−21.0, −0.5]	0.03	34.5	[−19.0, −3.0]	0.02
Males							
Size 4 (n=17)	37.5	35.5	[−3.5, 0.0]	0.08	28.0	[−18.0, 0 0]	0.55
Size 5 (n=13)	46.0	34.0	[−24.0, −5.0]	0.001	31.0	[−82.0, −1.0]	0.03

mask (fig. 1). Removal of air to the minimum effective volume generally decreased the pressure (fig. 1, table 2). On removal of the mask, intracuff pressure did not significantly exceed the initial pressure of the maximally inflated cuff when the smaller size was used; when the larger size was used, pressure at removal was significantly lower than the initial maximum pressure (fig. 1, table 2).

PRESSURE EXERTED ON THE PHARYNX

Friedman's two-way analysis of variance showed that pressures exerted on the pharynx by the mask at three times (initial maximum inflation, effective minimum inflation and on removal) were significantly different for size 4 in females ($P<0.05$) and for size 5 in males ($P<0.05$); there were no significant differences for the smaller sizes (table 2).

For the larger masks (size 4 in females and size 5 in males), removal of air from the maximally inflated cuff to the minimum effective volume significantly decreased the pressure exerted on the pharynx ($P<0.05$ in females; $P=0.001$ in males); pharyngeal pressure on removal remained lower than that with the initial maximally inflated cuff in both sexes ($P<0.05$ in both sexes).

There was no difference between the two sizes of masks in both sexes in pharyngeal pressure at minimum effective volume or on removal of the mask (table 2).

Discussion

MINIMUM EFFECTIVE VOLUME AND PRESSURE

Previous studies have shown that, when the cuff is inflated with the recommended maximum volume of air, intracuff pressure is initially more than 100 mm Hg, it increases steadily during anaesthesia and may reach 200 mm Hg or even greater on removal of the mask.[14–16] In our study, removal of air from the cuff to the minimum effective volume decreased intracuff pressure, and pressure on removal was similar to, or even lower than, that of an initial maximally inflated cuff (fig. 1; table 2). The volume of air in the cuff at removal was also not much greater than the recommended maximum volume (table 1). More importantly, removal of air from the cuff to the minimum effective volume also significantly decreased the pressure exerted on the pharynx; at removal of the mask, the pressure was either similar to or significantly lower than the initial pressure.

The pressure exerted on the pharynx by the mask is usually higher than that of mucosal capillary perfusion pressure when the cuff is inflated with the recommended maximum volume of air.[14] To reduce the pressure, O'Kelly, Heath and Lawes routinely inflated the cuff of a size 3 or 4 mask with a fixed volume of 10 ml and found that the pressure exerted on the pharynx was lower than capillary perfusion pressure.[15] However, if the cuff is deflated excessively, it may not prevent soiling of the larynx from fluid (such as regurgitated fluid) in the pharynx.[17] Therefore, it is desirable to inflate the cuff of the laryngeal mask with the minimum volume of air which provides a seal around the mask.

Several groups of researchers have investigated if removal of gas from the cuff of the laryngeal mask altered the incidence of pharyngeal discomfort after operation.[18–20] In two studies, removal of gas from the laryngeal mask to the minimum effective pressure decreased the incidence of sore throat after operation,[18 19] indicating that the pressure exerted on the pharynx was decreased by removal of gas. In contrast, in another study, when intracuff pressure was adjusted continuously to 30 mm Hg using a pressure controller, the incidence of postoperative sore throat was similar to that in another group of patients in whom intracuff pressure was adjusted to 180 mm Hg.[20]

The reason for these differences is not clear, but one possibility is that there is no clear correlation between intracuff pressure and pressure on the pharynx. Marjot showed that intracuff pressure increased as cuff volume increased, whereas the pressure exerted on the pharynx increased initially as the cuff was being inflated but started to decrease when the cuff was inflated further.[14] In our study, there was no clear relationship between intracuff pressure and pressure on the pharynx: the pressure exerted on the pharynx decreased during anaesthesia despite the increase in intracuff pressure (table 2). Therefore, maintenance of a low intracuff pressure may not always produce a low pressure on the pharynx.

APPROPRIATE SIZE OF THE LARYNGEAL MASK

There are a few factors which can be considered when selecting an appropriate size of laryngeal mask. First, the mask should provide an airtight seal during positive pressure ventilation. Second, the mask should not produce excessive pressure on the pharynx. Lastly, the mask should not be too large to insert.

Voyagis, Batzioulis and Secha-Doussaitou attempted to decide if the patient's age or weight was a better indicator for selecting the appropriate size of laryngeal mask.[6] They allocated patients to one of two groups; in one group, the size was selected based on the patient's sex (size 4 in females and size 5 in males); in the other group, the size was based on the patient's weight (size 3 in patients weighing less than 70 kg, size 4 for 70–90 kg and size 5 for more than 90 kg). They found that the mean peak inspiratory pressure at which airleak occurred was greater using the sex-related method compared with the weight-related method.[6]

In our study, a larger size (size 4 in females and size 5 in males) provided an airtight seal more frequently than a smaller size (size 3 in females and size 4 in males). There were no significant differences in the pressure exerted on the pharynx between the two sizes of masks in either sex (table 2). Lastly, it was always possible to insert the laryngeal mask. Therefore, we believe that in females, the size 4 is more appropriate than the size 3, and in males the size 5 than the size 4.

In summary, removal of air from the cuff of the laryngeal mask from the recommended maximum volume to the effective minimum volume reduced intracuff pressure and the pressure exerted on the pharynx. A larger size of the laryngeal mask (size 4 in females and size 5 in males) provided a better seal than a smaller mask (size 3 in females and size 4 in males) without producing a higher pressure on the pharynx.

Acknowledgement

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LABORATORY INVESTIGATIONS

Changes in mucociliary activity may be used to investigate the airway-irritating potency of volatile anaesthetics

A. CERVIN AND S. LINDBERG

Summary

We have examined the short-term effects of three volatile anaesthetics, halothane, isoflurane and desflurane, on mucociliary activity in the rabbit maxillary sinus *in vivo*. Mucociliary activity was recorded photoelectrically and the signal processed by fast Fourier transformation. Administration of 1.0 MAC of halothane, isoflurane or desflurane caused a temporary increase in mucociliary activity, with mean peak responses of 47.8 (SEM 13.0)%, 44.0 (9.6)% and 45.1 (23.7)% (*n*=6), respectively. The response to all three compounds was biphasic; an initial peak was observed within 2 min and a second peak at 3–8 min. The second response was not significant for halothane. In contrast, desflurane produced a significant second peak while the first was small and failed to reach significance. Halothane displayed an initial peak within 2 min which was blocked by atropine but not by the neurokinin 1 (NK1) receptor antagonist CP-99. The second peak at 3–5 min was less pronounced for halothane than for isoflurane or desflurane. The second peak was not affected by atropine pretreatment, but was blocked by pretreatment with CP-99. A combination of atropine and CP-99 pretreatment abolished the mucociliary response to halothane. Atropine pretreatment did not affect, whereas CP-99 significantly reduced, the response to desflurane. We conclude that the NK1-mediated response was most pronounced for desflurane which is considered the most airway irritating compound of the three. It is likely that the size of the NK1-mediated response reflects the airway-irritating properties of the volatile anaesthetic used. (*Br. J. Anaesth.* 1998; **80**: 475–480)

Keywords. anaesthetics volatile, halothane; anaesthetics volatile, isoflurane; anaesthetics volatile, desflurane; airway, mucosa; lung, trachea; rabbit

The mucociliary system is an important airway defence mechanism which removes inhaled debris and microorganisms. Impairment during anaesthesia may contribute to postoperative complications, such as pulmonary infection and atelectasis, which are particular problems in smokers.[1 2] Previous studies have shown anaesthesia to impair mucociliary function in humans[3] and other mammals,[4–7] and also *in vitro*.[8–12] Volatile anaesthetics such as halothane, enflurane and isoflurane, and i.v. anaesthetics such as thiopental, may be responsible for reduced mucociliary transport. In contrast with these studies, a recent investigation showed that halothane induced a short-term increase in mucociliary activity in the rabbit maxillary sinus followed by a reversible decrease in mucociliary activity.[13] The acceleration was probably part of a mucociliary defence reflex involving release of substance P (SP) from unmyelinated sensory fibres and a cholinergic efferent reflex mechanism.[14]

Desflurane is a new volatile anaesthetic. It is especially noted for its rapid elimination, but also for its irritating effect on the airways, causing coughing, apnoea, laryngospasm and salivation, thus making it less attractive for induction of anaesthesia.[15] Isoflurane is less irritating to the airways than desflurane, but more irritating than halothane.

The main aim of this study was to examine if different airway-irritating properties of anaesthetics are reflected in different responses in mucociliary activity, thus indicating whether or not this animal model would be useful as a tool for estimating the airway-irritating effect of future anaesthetic substances. Furthermore, by using pharmacological blockers, our aim was to study the mechanism responsible for the increase in mucociliary activity after exposure to halothane and desflurane.

Materials and methods

Experiments were performed in male and female adult New Zealand rabbits, weighing 2.2–3.1 kg (mean 2.6 kg). The animals were bred and housed in approved animal facilities, and the study was approved by the Committee of Animal Care and Use, Lund University. The animals were anaesthetized with urethane 2 g kg^{-1} i.m. as an initial dose, with an extra dose of 0.5 g kg^{-1} i.v. during operation. The facial artery was explored and a retrograde cannula (size 3 FG, Portex, UK) was inserted with its tip close to the maxillary artery. Details of the anaesthetic and surgical techniques have been published previously.[16] An i.v. cannula was inserted into one of the ear veins and perfused with 0.9% saline or 5.5% glucose at approximately 6–12 ml h^{-1}. The mucosa of the maxillary sinus was exposed via a trepanation of approximately 2×8 mm, which was covered immediately with a heated window, and sealed to the bone with bone wax (Ethicon, UK).

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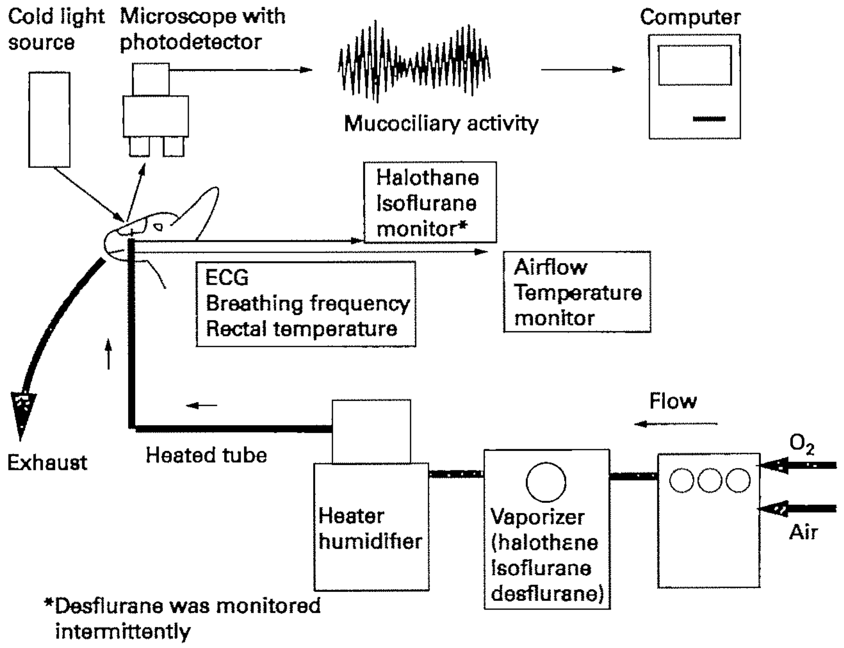
Cold light source
Microscope with photodetector
Mucociliary activity
Computer
Halothane Isoflurane monitor*
ECG Breathing frequency Rectal temperature
Airflow Temperature monitor
Exhaust
Heated tube
Flow
O_2
Air
Heater humidifier
Vaporizer (halothane Isoflurane desflurane)
*Desflurane was monitored intermittently

Figure 1 Schematic drawing of the experimental set-up. Gases were introduced into the maxillary sinus using a 2-mm syringe connected to the anaesthetic system. The temperature in the anaesthetic system was maintained at 31–35° C. (Modified and printed with permission of *Otolaryngology–Head and Neck Surgery* 1995; **112**: 714–722.)

Mucociliary activity (visible as flickering light reflections) was observed through a binocular microscope, the criterion of a functionally satisfactory preparation being visible transportation of small particles such as mucus clumps and cell debris. One of the eyepieces was switched to a phototransducer, and mucociliary activity recorded photoelectrically.[17] The mucociliary wave pattern was monitored continuously on an oscilloscope and analysed by fast Fourier transformation (FFT) on a PC (Hewlett-Packard Vectra 486DX2, 66 MHZ, France), equipped with an analogue–digital board (DAS 1401, Keithley Metrabyte, Taunton, MA, USA). The software used for FFT analysis was Viewdac (version 2.2.2, Keithley Data Acquisition Division, Taunton, MA, USA). The quality of the signal was assessed by its pattern on the oscilloscope combined with signal amplitude and frequency spectrum, as analysed and displayed by the computer program.

Mucociliary wave frequency was calculated every 10 s during challenge. Induced frequency changes were expressed as percentages of baseline mucociliary wave frequency (zero frequency level) immediately preceding the challenge. Rectal temperature was monitored, and body temperature was maintained at 37–38.5°C using a heating pad. Ventilatory frequency was recorded from the thorax with a tocotransducer (152 78B, Hewlett-Packard, Germany). For pulse registration an ECG was monitored continuously and recorded on file, together with respiratory frequency and mucociliary wave frequency.

An open Jackson–Rees anaesthetic system was used with vaporizers for halothane (Penlon Ltd, UK), isoflurane (Isotec 4, Cyprane Ltd, UK) and desflurane (Tec 6, BOC Ohmeda Ltd, UK). Halothane, isoflurane and oxygen concentrations were monitored continuously (Servo-Gas monitor 120, Siemens-Elema AB, Sweden). Desflurane concentration was monitored intermittently using a 5330 Agent Monitor (BOC Ohmeda Ltd, UK). The anaesthetic breathing system was connected to a 2-mm diameter syringe and introduced via the bone wax seal into the maxillary sinus. A heater–humidifier for anaesthetic gases (Dual Servo respiratory humidifier MR 600, Fischer and Paykel, New Zealand) was connected, and the temperature in the anaesthetic system was maintained at 31–35°C, which corresponds approximately to a nasal mucosal temperature of 34°C. Care was taken to direct the air stream directly towards the heated glass window and not towards the mucosa (fig. 1).

In blocking studies, bolus doses of halothane or desflurane 10 ml were administered into the nasal cavity via a small polyethylene catheter (3 FG, Portex Ltd, UK) which was inserted 20 mm into the nasal cavity via the ipsilateral nostril and secured. This method proved to be less technically demanding than that described above. The gas mixture was drawn from the anaesthetic system in airtight glass syringes and administered within 60 s. Boluses of air, halothane or desflurane delivered before the blockers were administered, and served as controls. All drugs were injected intra-arterially (i.a.) via a retrograde cannula in the maxillary artery.

Volatile anaesthetics were obtained from the following sources: halothane (ISC Chemicals Ltd, UK), isoflurane (Forene, Abbott Ltd, UK) and desflurane (Suprane, Kabi Pharmacia, Sweden). CP-99,994-1 (CP-99), a non-peptide substance P antagonist, selective for the tachykinin neurokinin-1 (NK1) receptor, was a gift from Pfizer Inc. (CT, USA). CP-99 was dissolved in sterile water to a stock solution of 1 mg ml^{-1}. Atropine, a muscarinic receptor antagonist, contains atropine sulphate 2 mg ml^{-1} in saline (ACO, Sweden). Substance P (SP, Peninsula Laboratories Europe Inc., St Helens, UK) was dissolved in 0.5% albumin to 100 µg ml^{-1}. Methacholine chloride 10 mg ml^{-1} in saline was obtained from Apoteksbolaget (Sweden).

EXPERIMENTAL PROCEDURES

Six rabbits were used to investigate the effects of halothane, isoflurane and desflurane. All animals

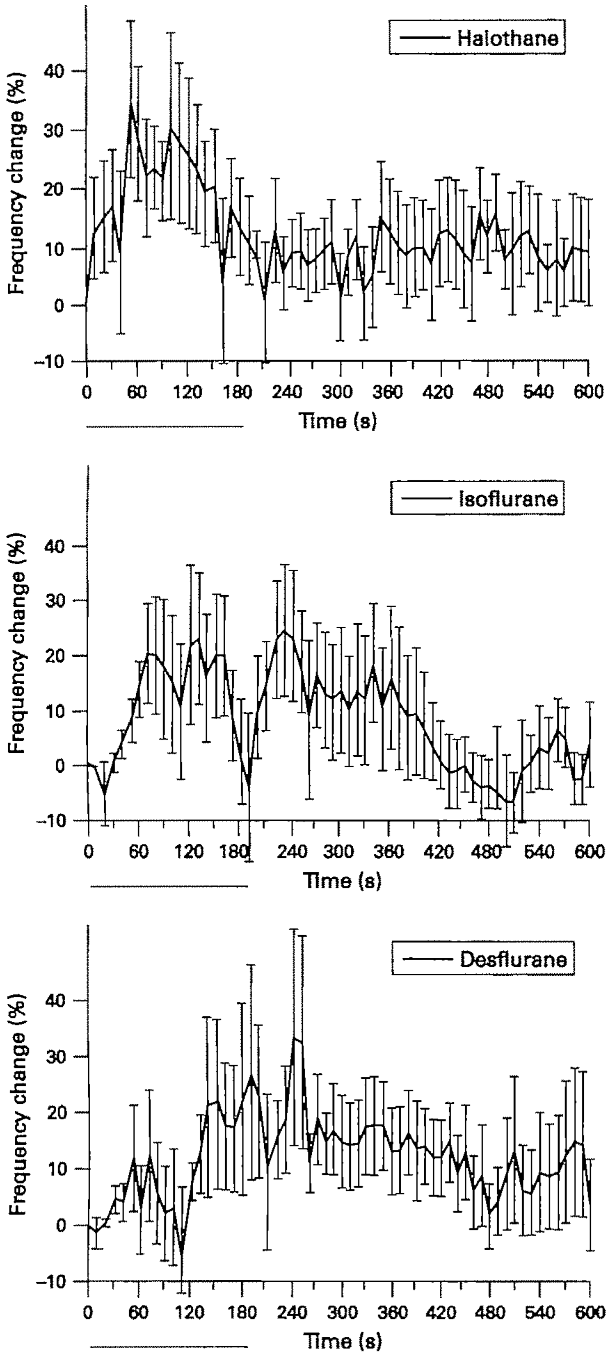

Figure 2 Time course curves over 10 min after 3 min exposure to 1.0 MAC of halothane, isoflurane or desflurane delivered into the maxillary sinus. Zero frequency levels were mean 15.6 (SD 4.4) Hz, 17.4 (4.4) Hz and 17.1 (4.9) Hz for halothane, isoflurane and desflurane, respectively (n=6). Horizontal bars indicate challenge with respective anaesthetic.

received all anaesthetics. A period of at least 60 min was allowed to elapse between exposures, and the order of exposure varied. Two rabbits started with halothane, two with isoflurane and two with desflurane, and the following exposures were also varied to create a similar exposure order for all three compounds. The anaesthetics were introduced into the maxillary sinus when the anaesthetic system was saturated at an airflow of 0.5 litre min^{-1}. The maxillary sinus was exposed for 3 min. Airflow alone served as a control. The concentration of anaesthetics was 1.0 MAC, which corresponds to 1.1% for halothane,[18] 2.0% for isoflurane[19] and 8.9% for desflurane.[20]

Five rabbits were pretreated with atropine 0.2 mg kg^{-1} i.a and within 5 min exposed intranasally to a 10-ml bolus dose of 1.1% halothane. Eight rabbits were used (five of which had been used in previous experiments but allowed a 60-min resting period). To confirm that cholinergic block had subsided, the preparation was challenged with the cholinergic agonist methacholine (0.1 μg/kg bodyweight i.a.). If an appropriate response occurred, the experiment was continued. The selective NK1 receptor antagonist CP-99 0.1 mg kg^{-1} was given i.v. Satisfactory block of the NK1 receptor was achieved when the response to SP 0.1 μg kg^{-1} i.a. was abolished. Halothane was then administered (at least 15 min after SP challenge) as a bolus dose of 10 ml into the ipsilateral nostril.

Six of the previously used animals were given another 60-min rest period and then re-tested with SP to confirm NK1 block. If this was found to be sufficient, atropine 0.2 mg kg^{-1} was administered i.a. and within 5 min halothane was administered as a bolus dose of 10 ml into the ipsilateral nostril.

In a separate series of eight rabbits, the blocking studies were repeated as described above using 9% desflurane, delivered as a bolus dose of 10 ml into the ipsilateral nasal cavity.

Results are expressed as mean (SEM), with the exception of baseline mucociliary wave frequency (zero frequency level) which is expressed as mean (SD). Peak response values and area under the curve (AUC) were used for statistical evaluation. All rabbits served as their own control. The results were analysed using two-way ANOVA repeated measurements and, when appropriate, Student's t test for paired data. $P<0.05$ was considered significant. P values refer to both peak responses and AUC, unless otherwise stated. The software used for statistical analysis was Statview version 4.1 and 4.51 (Abacus Concepts, Berkeley, CA, USA).

Results

An airflow of 0.5 litre min^{-1} or bolus injections of 10 ml of air into the nose did not influence mucociliary activity compared with spontaneous activity (data not shown). There was no effect on heart rate for any of the anaesthetics. All three anaesthetics increased mucociliary activity. The mean peak response was 47.8.3 (SEM 13.0)% (n=6, $P<0.05$) for halothane, 44.0 (9.6)% (n=6, $P<0.05$) for isoflurane and 45.1 (23.7)% (n=6) for desflurane. The peak response for desflurane was not significant, but AUC was significant ($P<0.05$) (fig. 2). There were no differences between the three compounds regarding the maximum effect or AUC. However, the peak effect of halothane was achieved in 60 s whereas the isoflurane response was biphasic, peaking at 120 s and 240 s.

The peak response to desflurane was also delayed, and appeared at approximately 240 s. Comparing responses during the first 2 min, the halothane response was significantly greater than that for desflurane ($P<0.05$, n=6), while no significant differences were found between isoflurane and desflurane or halothane and isoflurane. The response to isoflurane and desflurane displayed a biphasic time course which was not observed for halothane. In some cases the initial response was associated with a

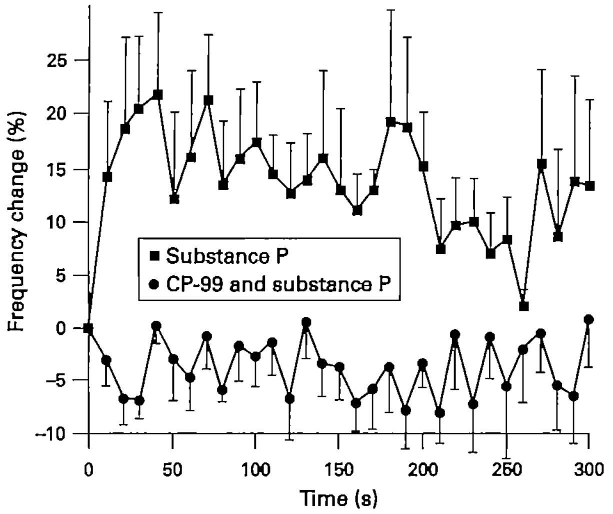

Figure 3 Time course curve for the response to substance P 0.1 µg kg^{-1} before and after pretreatment with CP-99. Zero frequency levels were mean 17.6 (SD 1.4) Hz and 17.5 (1.4) Hz, respectively (n=8, P<0.05).

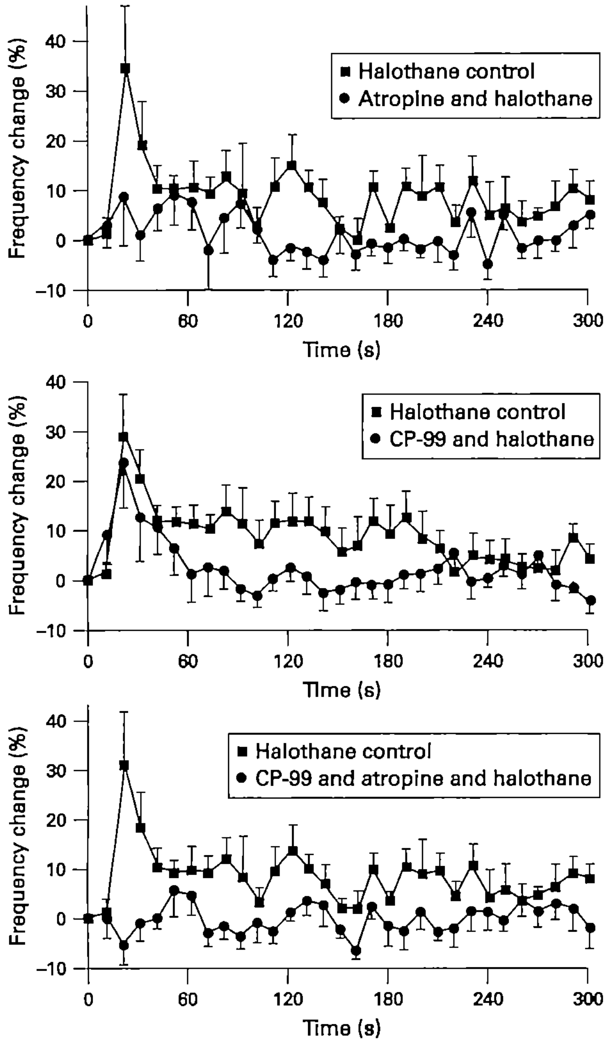

Figure 4 Time course curve for halothane 1.0 MAC injected as a bolus dose of 10 ml into the ipsilateral nostril, before and after pretreatment with atropine, CP-99 and combined pretreatment with atropine and CP-99. Zero frequency level was 14.7 (SD 4.3) Hz (n=6) in the halothane group, 13.1 (1.8) Hz (n=8) in the atropine pretreatment group, 18.1 (2.3) Hz (n=6) in the CP-99 pretreatment group and 14.7 (5.0) Hz (n=6) in the combined pretreatment group.

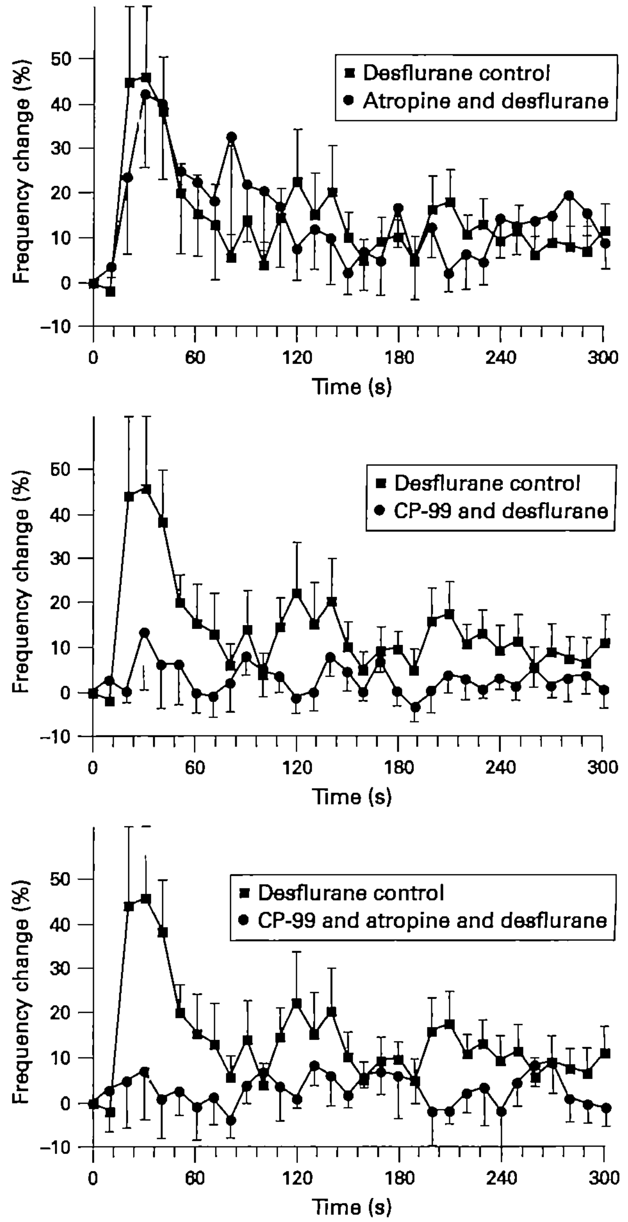

Figure 5 Time course curve for 1.0 MAC of desflurane injected as a bolus dose of 10 ml into the ipsilateral nostril, before and after pretreatment with atropine, CP-99 and combined pretreatment with atropine and CP-99. Zero frequency level was 15.9 (SD 1.6) Hz (n=8) in the desflurane group, 13.1 (1.8) Hz (n=8) in the atropine pretreatment group, 14.2 (2.3) Hz (n=8) in the CP-99 pretreatment group and 11.9 (0.8) Hz (n=7) in the combined pretreatment group

short period of apnoea. There were no differences in duration or incidence of apnoea between the anaesthetics.

In previous studies in the same animal model, atropine did not effect mucociliary activity.[20] In our study the effect of the selective NK1 receptor antagonist, CP-99, was evaluated and shown to have no effect on mucociliary activity compared with saline but was effective in blocking the response to SP (n=8, P<0.05) (fig. 3). There were no significant differences in peak response between nasal and maxillary administration of halothane and desflurane, although there was a tendency towards a higher peak response when desflurane was administered intranasally.

In the halothane blocking experiments, pretreatment with atropine reduced the peak response from 44.8 (9.2) to 23.3 (6.4)% (P=0.11 for peak response and P=0.13 for AUC, n=5) with the response at 3–5 min unaffected (fig. 4). Pretreatment with CP-99 altered the response to halothane, such that the initial peak response was unaffected by CP-99 while the response at 3–5 min was reduced (peak response P=0.8, and for AUC P=0.09, n=8) (fig. 5). A combination of atropine and CP-99 significantly reduced the response to halothane (P<0.01, n=6) for both peak response and AUC (fig. 5).

Desflurane 9% injected into the nasal cavity increased mucociliary activity by 71.9 (10.3)% (P<0.001, n=8) compared with air controls (fig. 5). Pretreatment with atropine had no effect on the response to desflurane; peak response was 69.3 (20.3)% (ns, n=8) compared with desflurane alone. Pretreatment with CP-99 significantly reduced the response to desflurane; peak response was 26.6 (10.7)% (P<0.05 for peak response and P<0.01 for AUC) compared with desflurane alone. The peak response after combined pretreatment with atropine and CP-99 was significantly reduced to 32.3 (7.0)% (P<0.05), however it did not differ from block with CP-99 alone. The remaining peak response, but not AUC, after combined block was significantly increased compared with controls exposed to air (P<0.01 for peak response and P=0.2 for AUC).

Discussion

Previous investigations, both *in vivo* and *in vitro*, have focused on the slowing effect of halothane and other volatile anaesthetics on ciliary beat frequency. Physiological studies, with the possibility of recording rapid changes in mucociliary activity, have been lacking. It has been shown recently in the same animal model that short exposure to halothane stimulates mucociliary activity.[13] Our study focused on the mechanisms involved in short-term exposure to volatile anaesthetics.

Regulation of mucociliary function in the upper airways is complex and mediated partly by neuronal mechanisms. Previous investigations have shown airway-irritating substances such as cigarette smoke and ammonia vapour to induce an increase in mucociliary activity. This response to noxious stimuli was partly blocked by atropine and partly blocked by a substance P antagonist.[14 21] Further investigations on which of the different neurokinin receptors were involved in the response revealed that tachykinin-evoked acceleration of mucociliary activity was mediated by NK1 receptors,[22] providing the rationale for choosing the NK1 receptor antagonist CP-99 in this study.

Exposure of the maxillary sinus to halothane, isoflurane and desflurane resulted in a transient increase in mucociliary activity. There were no significant differences in maximal responses to the anaesthetics. In the halothane studies, the initial peak (within 2 min) was the maximal response, in contrast with the desflurane response where the immediate response was small compared with the later response at 2–5 min. In blocking studies, nasal administration was used and a biphasic response was not observed. However, comparing figures 5 and 4, it is evident that atropine, in contrast with the NK1 antagonist, was not effective in blocking the immediate response to desflurane. On the contrary, in the halothane experiments, atropine was effective in blocking the initial response whereas the NK1 antagonist had little effect. These data suggest that the effect of the more airway irritating compound was mediated mainly via the NK1 receptor in contrast with the halothane experiments where the response was mediated mainly via cholinergic mechanisms. The mechanism for the increased sensitivity of airway sensory C-fibres to desflurane compared with halothane is not known but may be related to possible differences in the effects of Ca^{2+} homeostasis, as it has been shown recently that the capsaicin receptor is a non-selective ion channel.[23] Another speculation is that tissue pH may be reduced by desflurane leading to increased sensitivity of the vanilloid receptors on sensory C-fibres as the receptor is sensitive to decreased tissue pH.[23]

Desflurane is a new inhalation anaesthetic with physical properties which distinguish it from isoflurane and halothane. Data from the literature support the view that desflurane stimulates the sympathetic nervous system, and hypertension and tachycardia have been observed,[24] in addition to coughing, apnoea, laryngospasm and salivation at concentrations of 6–8%.[25] Desflurane is thus less suitable for induction of anaesthesia than halothane, which has little or no effect on the sympathetic nervous system. In blocking studies with desflurane, a biphasic response was not as evident as in previous experiments, which may be because the challenge was via the nose instead of the maxillary sinus mucosa. It was also noted that there was a tendency towards a higher maximal response to desflurane during nasal exposure than after administration into the maxillary sinus, although this was not significant. A denser distribution of sensory C fibres in the nose than in the maxillary sinus could provide an explanation of the increased response to desflurane, although to our knowledge there are no histological studies supporting this hypothesis.

In this animal model, sympathetic nerve stimulation has been found to increase mucociliary activity.[26] The influence of the sympathetic nervous system was not evaluated in this study. It is possible that exposure to volatile anaesthetics initiates a sympathetic reflex, especially exposure to desflurane. There were no significant changes in heart rate and the combination of cholinergic and NK1 block was sufficient to abolish the response to halothane. However, the remaining response to desflurane after pretreatment with atropine and CP-99 could be explained by a sympathetic reflex mechanism, although there was no effect on heart rate. Future studies with a ß-antagonist are warranted.

Anaesthesia and analgesia are prerequisites for this experimental model. Urethane provides both, with a minimum effect on respiration and circulation. A possible interaction with the anaesthetics used in the different challenges cannot be excluded. However, in a previous study using this animal model, urethane was compared with pentobarbital. Both drugs were given i.v. and the latter had a marked effect on mucociliary activity whereas urethane had little or no effect.[16] Other investigators have shown urethane to have no effect on respiratory fluids.[27]

Administration of gases directly into the maxillary sinus where the signal from the mucociliary system is picked up can easily disturb the delicate interaction between the beating cilia and mucus and the periciliary layer (the medium in which the cilia beat). In a previous study it was shown that airflow rates exceeding 0.5 litre min^{-1} caused a reduction in mucociliary activity.[13] Therefore, the flow rate used in the experiments comparing the effects of halothane, isoflurane and desflurane was not allowed to exceed 0.5 litre min^{-1}.

In summary, in this animal model, the mucociliary system responded readily to the different anaesthetic gases. The response consisted of both a cholinergic pathway and an NK1 receptor-mediated pathway, probably by stimulation of afferent unmyelinated C fibres and via cholinergic effector neurones, combined with the release of SP from the peripheral endings of C fibres. The NK1-mediated response, which was greater after desflurane administration than halothane, may reflect the airway-irritating effects of this volatile anaesthetic. Our experimental model provides a potential tool for investigating the airway-irritating effects of volatile anaesthetics.

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Cardiovascular effects of concomitant administration of isoflurane and nicorandil in dogs

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Summary

Nicorandil, a new K_{ATP} channel opener, is used in clinical practice for anti-anginal therapy. It exhibits vasodilator properties as does the halogenated anaesthetic isoflurane. We have examined the cardiovascular effects of increasing concentrations of isoflurane after administration of nicorandil in 10 adult beagle dogs anaesthetized with thiopental and whose lungs were ventilated mechanically. During surgery, anaesthesia was maintained with 1.0–1.5% isoflurane. A left thoracotomy was performed and the heart suspended in a pericardial cradle. Monitoring included: ECG; aortic, left ventricular, arterial, central venous and pulmonary artery pressures; cardiac output; coronary flow; and segmental length in the apical region. After surgery, isoflurane anaesthesia was set at an end-tidal concentration of 1.05% (1 MAC) and measurements obtained; these were repeated with 1.4%, 1.75%, 2.1% and 1.05% isoflurane concentrations after appropriate stabilization periods. Nicorandil (100 μg kg^{-1} bolus, 25 μg kg^{-1} min^{-1} infusion) was begun and a second dose–response study of isoflurane was obtained as before. Blood samples were obtained for measurement of concentrations of nicorandil. Systolic ventricular function was assessed by systolic shortening (%SS) and preload recruitable stroke work (PRSW). Increasing isoflurane concentration produced decreases in heart rate, systolic pressure, cardiac output, %SS and PRSW. Nicorandil produced a slight decrease in systolic arterial pressure (10 and 15 mm Hg after 1.05% and 2.05% isoflurane) and a slight increase in heart rate (10 and 5 beat min^{-1} after 1.05% and 2.05% isoflurane). Preload, assessed by end-diastolic length, decreased. Coronary blood flow increased with infusion of nicorandil. Left ventricular function was not affected by infusion of nicorandil. We conclude that nicorandil has only minor vaso/venodilatory effects in the presence of isoflurane. Ventricular function was not altered by infusion of nicorandil. (*Br. J. Anaesth.* 1998; **80**: 481–487)

Keywords: anaesthetics volatile, isoflurane; pharmacology, nicorandil; heart, nicorandil; dog; heart, myocardial function, cardiovascular system, effects

Nicorandil, an ATP-sensitive potassium (K_{ATP}) channel opener, is a potent vasodilator whose anti-anginal and anti-ischaemic actions can be attributed to its profound vasodilatory effects on the arterial and venous circulation[1] and to a specific cardioprotective effect via opening of the K_{ATP} channel during ischaemia.[2] This vasodilator has little effect on cardiac contractility, produces increases in coronary blood flow and decreases in systemic arterial pressure.[2] The mechanism of action is two-fold: a nitrate-like effect mediated by an increase in cyclic GMP and a selective increase in K^+ conductance of smooth muscle cell membrane.[1] Nicorandil effectively unloads the heart, producing a decrease in peripheral resistance and an increase in venous capacitance.[3 4]

Isoflurane, a halogenated anaesthetic agent, depresses myocardial contractility[5] and acts as a dose-related vasodilator.[6] Increasing the concentration of isoflurane produces dose-related decreases in systemic pressure, heart rate and contractility.[5] The effects of isoflurane have been attributed in part to alterations in trans-sarcolemmal calcium flux.[7] Moreover, vasodilatory[8 9] and cardioprotective[10–12] properties of isoflurane seem to be mediated in part via opening of the K_{ATP} channel.

With the possibility of an increase in the number of anginal patients receiving nicorandil presenting for surgery, we have examined the cardiovascular effects of nicorandil on the response to graded concentrations of isoflurane on haemodynamic and ventricular variables to determine if there is an additive action of isoflurane and nicorandil.

Materials and methods

The study conformed to the UK Animals Act (Scientific Procedures, 1986). We studied 10 adult beagle dogs of both sexes (weight 10–12 kg), premedicated with morphine 1.0 mg kg^{-1} i.m. and anaesthetized with thiopental 15 mg kg^{-1} i.v. After tracheal intubation the animals were placed on their right side and underwent mechanical ventilation (40% oxygen in nitrogen). Anaesthesia was maintained with 1.0–1.5% isoflurane. Inspiratory and

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end-tidal gas concentrations were measured continuously (gas analyser M1025A, Hewlett Packard, Bracknell, UK) and mechanical ventilation adjusted to maintain end-tidal carbon dioxide concentration at 4.5–5.5%. Mid-oesophageal temperature was maintained at 36–37°C using a Servo-controlled heating element incorporated into the operating table. Hetastarch 5 ml kg^{-1} h^{-1} was infused continually via an i.v. cannula inserted into the inferior vena cava via a vein in the left hind leg. Left thoracotomy was performed, the fifth and sixth ribs excised, and the heart suspended in a pericardial cradle.

Monitoring included limb lead II of the ECG (subcutaneous needle electrodes); a piece of thin rubber tubing around the inferior vena cava distal to the right atrium for caval occlusion; a 7-French gauge pulmonary artery catheter (Swan-Ganz, American Edwards Laboratories, Anasco, Puerto Rico) inserted via the left jugular vein for measurement of central venous pressure, pulmonary artery pressure and cardiac output; and a 8-French gauge rigid fluid-filled cannula in the descending aorta, inserted via the femoral artery and connected to a pressure transducer (Druck, Druck Ltd, Groby, Leicester, UK) for measurement of systemic arterial pressure during surgery. Two micromanometer-tipped 8-French gauge catheters (Millar, Houston, TX, USA) were used to measure pressure in the ascending aorta (inserted via the left common carotid artery to within 1 cm of the aortic valve) and in the left ventricle (inserted via a stab wound in the apical dimple); a Doppler flow probe (Triton, San Diego, CA, USA) was placed around the left anterior descending coronary artery (LAD); and a pair of piezoelectric crystals (Triton, San Diego, CA, USA, 2 mm in diameter, 5 MHz) for ultrasonic measurement of segmental length were implanted parallel to the minor axis, in the apical region, in an area depending on the LAD blood supply. These were implanted in the subendocardium approximately 10 mm apart through epicardial stab wounds.

After surgery isoflurane was adjusted to 1.05% (1 MAC) end-tidal concentration. After a 30-min stabilization period, the first measurements were obtained. End-tidal isoflurane concentration was increased to 1.4% (1.3 MAC) and the preparation allowed to stabilize for 20 min. Further measurements were recorded. Thereafter measurements were obtained at 1.75% (1.7 MAC) and 2.1% (2 MAC) isoflurane, allowing the preparation to stabilize at each stage. The isoflurane concentration was then decreased to 1.05% (1 MAC) and the preparation allowed to stabilize for 30 min, with measurements obtained at the end of this period. Nicorandil (100 µg kg^{-1} bolus, 25 µg kg^{-1} min^{-1} infusion) (Merck KGaA, Darmstadt, Germany, dissolved in NaCl 0.9% (w/v)) was infused into the vein in the hind leg and measurements obtained after 30 min; thereafter isoflurane was increased in a stepwise manner as before, with measurements obtained at each stage.

Blood samples were obtained just before (T0), 30 min after infusion of nicorandil (T1) and at the end of the study (T2) for measurement of plasma concentrations of nicorandil.

All sets of measurements consisted of: (1) cardiac output measured in triplicate using thermodilution (COM-2 Baxter, Santa Ana, USA), (2) steady state haemodynamic variables, and (3) recordings during caval occlusion (obtained by pulling the rubber tubing around the inferior vena cava for 8–10 s). Steady state haemodynamic variables were recorded for 5 s and caval occlusion data for 15 s. All measurements were made during expiratory apnoea.

MEASUREMENT OF NICORANDIL CONCENTRATIONS

Plasma concentrations of nicorandil were measured chromatographically. Blood samples were collected in test tubes containing lithium heparinate. Alkalinized plasma (2 ml), spiked with nicotinoylamidopropyl nitrate 2.5 ng ml^{-1} (SG 89, Merck KGaA, Darmstadt, Germany) as an internal standard, was

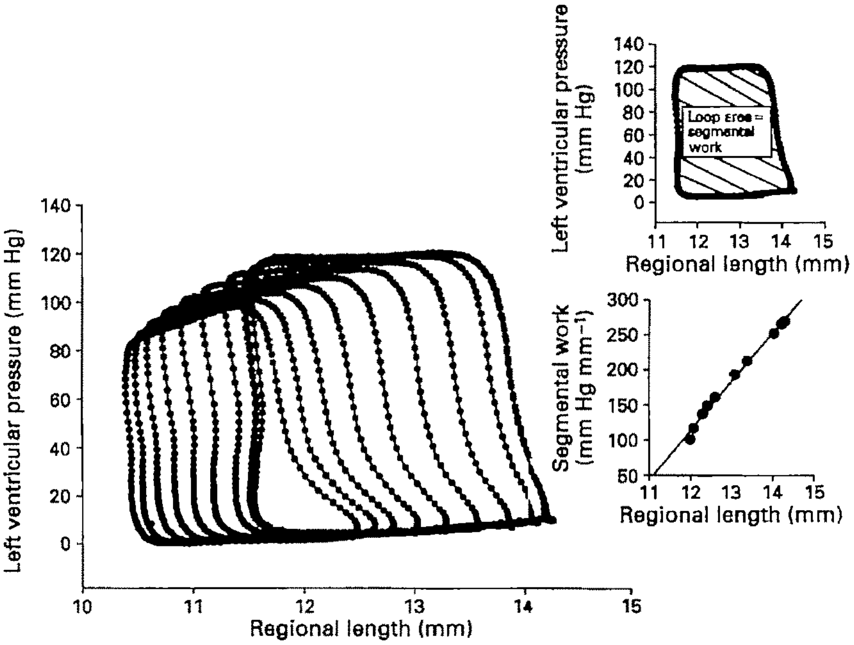

Figure 1 Series of pressure–length loops obtained during caval occlusion Inset top: single pressure–length loop representing segmental stroke work. Inset bottom: linear relationship between segmental stroke work and segmental end-diastolic length.

extracted with ethyl acetate. The organic phase was washed alternatively with acid and alkaline solutions and then evaporated to dryness under a nitrogen stream. The residue was dissolved in 100-µl mobile phase and 10 µl were injected onto a Hewlett Packard 1090 liquid chromatograph equipped with a Lichrosorb RP 18 (5 µm) column (60 mm, 3 mm) and UV detector (254 nm). Elution was moved at isocratic mode (1.5 ml min^{-1}) by a H_2O:acetonitrile:borate HCl buffer 0.15 mol litre^{-1}, pH 8.00 (75–15–10 vol./vol. mixture). The areas were integrated with a HP 3390 integrator and correlated to a standard calibration curve prepared with a reference nicorandil compound (SG-75 Merck). Analytical characteristics for extraction were recovered at 94.4% (n=20); the coefficient of variation for within-day precision was 3.6% (n=10), sensitivity was 6.0 ng ml^{-1} and the method was linear over the range 6–200 ng ml^{-1}.

DATA COLLECTION

ECG, pressures (aortic, left ventricular, arterial), coronary flow and regional dimension signals were converted using an analogue–digital converter (AT-MIO-16, National Instruments Corporation, Austin, TX, USA) and displayed continuously on an IBM AT personal computer using the real-time mode of software designed in this department. Data were sampled at a frequency of 500 Hz and stored on hard disc.

DATA ANALYSIS

Data analysis was performed on an IBM AT personal computer using the play-back mode of the above software. Peak positive left ventricular pressure dP/dt was obtained by electronic differentiation of the LV pressure signal. End-diastole was defined as the first upward (positive) deflection of the left ventricular dP/dt signal. End-systole was defined at peak negative dP/dt.

All length measurements were normalized to an initial value of end-diastolic length of 10 mm at control. The following definitions were used to quantify regional wall motion: EDL=end-diastolic length; ESL=end-systolic length. Systolic shortening (%SS) was defined as follows:

$$\%SS=(EDL-ESL)/EDL\times 100$$

Segmental stroke work (SW) was calculated by electronic integration of left ventricular pressure (P) and segmental length (L) over the entire cardiac cycle[13]:

$$SW=\int P\times dL$$

SW and EDL were fitted using linear regression to the equation:

$$SW=Msw(EDL-Lw)$$

where Msw=slope of the preload recruitable stroke work (PRSW) and Lw=x-intercept. The concept of preload recruitable stroke work is based on a linear relationship between myocardial work and myocardial preload, as assessed by the end-diastolic dimension. Myocardial work or segmental stroke work is calculated as the area of the pressure–length loop, that is integration of left ventricular pressure (P) and segmental length over the entire cardiac cycle. By occluding the inferior vena cava (caval occlusion) a series of pressure–length loops can be obtained whose areas can be plotted against their end-diastolic lengths. This is a linear relationship and gives the slope of the preload recruitable stroke work (Msw).

Table 1 Effects of isoflurane (I) and isoflurane with nicorandil (I+N) on systemic haemodynamics (mean (SEM)). HR=Heart rate; SAP=systolic arterial pressure; LVEDP=left ventricular end-diastolic pressure, PAP=pulmonary arterial pressure; CVP=central venous pressure; CO=cardiac output; COF=coronary flow; Tau=time constant of relaxation; Iso. effect=ANOVA within-subject analysis for the isoflurane factor; Nic. effect=ANOVA within-subject analysis for the nicorandil factor

	Isoflurane concentration (%)					
	1.05	1.4	1.75	2.1	Iso. effect	Nic. effect
HR (beat min^{-1})						
I	139 (9)	133 (9)	129 (9)	131 (8)	<0.001	<0.05
I+N	148 (10)	144 (8)	141 (7)	136 (6)		
SAP (mm Hg)						
I	121 (4)	109 (2)	99 (2)	87 (2)	<0.001	<0.001
I+N	110 (4)	88 (2)	82 (3)	70 (3)		
LVEDP (mm Hg)						
I	6.6 (1.2)	7.2 (1.4)	6.6 (1.3)	6.5 (0.9)	ns	ns
I+N	4.9 (0.8)	4.7 (0.4)	5.0 (0.3)	5.8 (0.6)		
PAP (mm Hg)						
I	19.3 (1.2)	18.6 (0.8)	17.6 (1.2)	17.6 (0.6)	<0.05	ns
I+N	17.4 (0.7)	15.7 (0.7)	15.2 (0.5)	15.4 (0.7)		
CVP (mm Hg)						
I	5.3 (0.9)	6.2 (1.0)	6.2 (0.9)	6.4 (0.7)	<0.001	ns
I+N	5.2 (0.8)	5.7 (0.7)	6.4 (0.7)	6.9 (0.8)		
+dP/dtmax (mm Hg s^{-1})						
I	2607 (200)	2119 (127)	1766 (108)	1432 (67)	<0.001	<0.001
I+N	2267 (144)	1686 (122)	1544 (117)	1163 (63)		
−dP/dtmax (mm Hg s^{-1})						
I	2786 (165)	2403 (99)	2056 (100)	1666 (65)	<0.001	<0.05
I+N	2543 (169)	1834 (81)	1588 (120)	1118 (105)		
CO (litre min^{-1})						
I	2.6 (0.2)	2.4 (0.1)	2.1 (0.1)	1.8 (0.1)	<0.001	ns
I+N	2.4 (0.1)	2.4 (0.1)	2.3 (0.1)	1.9 (0.1)		
COF (Hz×10^2)						
I	15.7 (2.0)	16.0 (1.9)	15.5 (1.7)	15.0 (1.4)	ns	<0.05
I+N	19.7 (2.3)	19.2 (2.5)	20.5 (2.6)	20.2 (2.6)		
Tau (ms)						
I	25.8 (1.8)	28.0 (1.8)	27.6 (1.6)	28.5 (1.4)	ns	<0.05
I+N	24.9 (1.4)	23.7 (1.1)	24.1 (1.2)	25.9 (1.1)		

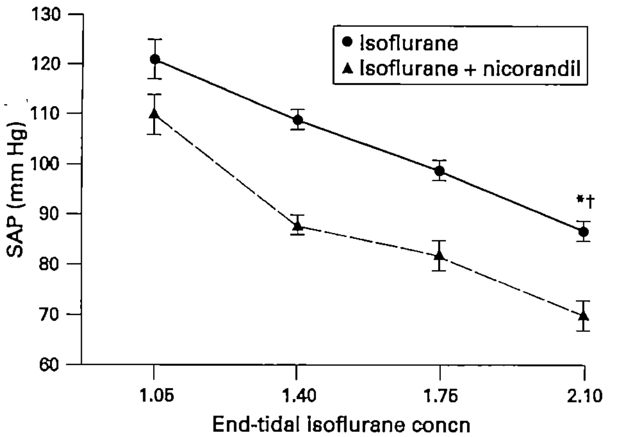

Figure 2 Dose–response of systolic arterial pressure (SAP) to increasing concentrations of isoflurane after administration of isoflurane alone or combined administration of isoflurane and nicorandil. $^*P<0.05$, ANOVA within-subject analysis for the isoflurane factor; $^†P<0.05$, ANOVA within-subject analysis for the nicorandil factor.

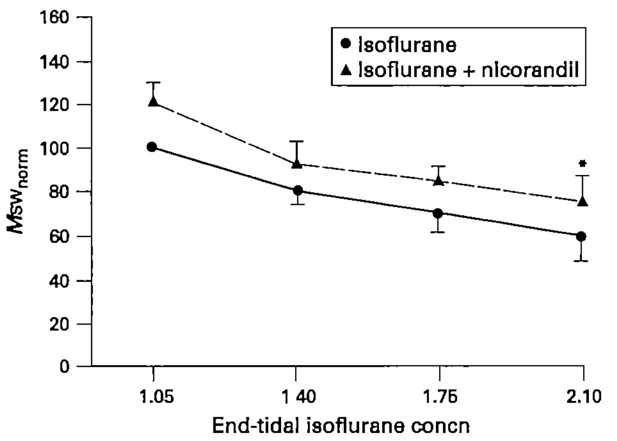

Figure 3 Dose–response of $M\mathrm{sw}_{\mathrm{norm}}$ to increasing concentration of isofluranes after administration of isoflurane alone or combined administration of isoflurane and nicorandil. $^*P<0.05$, ANOVA within-subject analysis for the isoflurane factor.

This assessment of ventricular contractility is independent of heart rate and loading status. It represents a linearization of the Frank–Starling relation. In our studies the linear correlation coefficient was greater than 0.90 in all measurements. Figure 1 shows an example of the series of pressure–length loops obtained during caval occlusion and the linear relationship obtained between segmental stroke work and end-diastolic length.

$M\mathrm{sw}$ and %SS were expressed as $M\mathrm{sw}_{\mathrm{norm}}$ and $\%\mathrm{SS}_{\mathrm{norm}}$ (isoflurane alone values were normalized to those obtained at the first measurement. Isoflurane and nicorandil measurements were normalized to those obtained at 1.05% isoflurane just before infusion of nicorandil).

STATISTICAL ANALYSIS

All values are expressed as mean (SEM). Data were analysed using SPSS (SPSS for Windows, release 7, SPSS Inc., Chicago, IL, USA). Two different factors (isoflurane concentration (four levels), drug (two levels)) were analysed using two-way ANOVA for repeated measurements. Changes within each factor were considered statistically significant when $P<0.05$. A paired *t* test was used to compare the first measurement obtained at 1.05% isoflurane and measurements obtained at the same isoflurane concentration before infusion of nicorandil. This was done to check that variables had returned to baseline values after the initial increases in isoflurane concentration.

Results

One dog was excluded from the study because of surgical problems. Therefore, all data are from the remaining nine dogs.

Table 1 shows the dose–response to isoflurane, before and after infusion of nicorandil, on systemic haemodynamic variables. There were no significant differences between measurements at 1.05% isoflurane and the return measurement at 1.05% isoflurane before infusion of nicorandil for all variables. Increasing the concentration of isoflurane decreased heart rate. Addition of nicorandil shifted the heart rate dose–response to isoflurane upwards, with higher heart rate values at all concentrations of isoflurane. Systolic arterial pressure (fig. 2) decreased with increasing isoflurane concentration (121 (4) to 87 (2) mm Hg at 1.05% and 2.1% isoflurane, respectively) with concurrent administration of nicorandil shifting the systolic arterial pressure dose–response to isoflurane downwards (110 (4) to 70 (3) mm Hg at 1.05% and 2.1% isoflurane, respectively). Central venous pressure increased with isoflurane concentration; addition of nicorandil had no effect. Global indices of ventricular function (+d*P*/d*t*max and −d*P*/d*t*max) decreased with increasing isoflurane

Table 2 Effects of isoflurane (I) and isoflurane with nicorandil (I+N) on regional function (mean (SEM)). EDL=End-diastolic length; $\%\mathrm{SS}_{\mathrm{norm}}$=systolic shortening normalized to the values obtained at 1.05% isoflurane and at 1.05% isoflurane just before infusion of nicorandil. $M\mathrm{sw}_{\mathrm{norm}}$=slope of preload recruitable stroke work normalized to the values obtained at 1.05% isoflurane and at 1.05% isoflurane just before infusion of nicorandil. Iso. effect=ANOVA within-subject analysis for the isoflurane factor; Nic. effect=ANOVA within–subject analysis for the nicorandil factor

	Isoflurane concentration (%)				ANOVA	
	1.05	1.4	1.75	2.1	Iso. effect	Nic. effect
EDL (mm)						
I	10.0	10.2 (0.1)	10.3 (0.1)	10.4 (0.2)	<0.05	<0.05
I+N	9.8 (0.2)	9.7 (0.2)	9.8 (0.2)	9.9 (0.3)		
$\%\mathrm{SS}_{\mathrm{norm}}$						
I	100	88 (2)	79 (4)	70 (5)	<0.001	ns
I+N	108 (6)	99 (6)	86 (7)	76 (5)		
$M\mathrm{sw}_{\mathrm{norm}}$						
I	100	81 (7)	71 (9)	60 (11)	<0.001	ns
I+N	120 (11)	92 (11)	86 (7)	76 (12)		

Table 3 Plasma concentrations of nicorandil (mg litre^{-1}). *$P<0.05$ compared with concentration at T1

	Time		
	T0	T1	T2
Mean (SEM)	0	0.52 (0.04)	0.99 (0.13)*
Range	0	0.31–0.68	0.4–1.4

concentration; this was accentuated in the presence of nicorandil. Increasing the concentration of isoflurane decreased cardiac output. Addition of nicorandil had no effect. There was no change in coronary flow at any concentration of isoflurane, however, coronary flow increased in the presence of nicorandil. The time constant of isovolumic relaxation (tau) remained unchanged with increasing isoflurane concentration but decreased with addition of nicorandil. Regional function data are summarized in table 2. Initial measurements of %SS and EDL at 1.05%, before infusion of nicorandil, differed significantly from the final measurements at 1.05%. %SS recovered to 85 (5)% and EDL remained unchanged from the measurement at 2.1% isoflurane. Increasing the isoflurane concentration increased end-diastolic length (10 to 10.4 (0.2) mm at 1.05% and 2.1% isoflurane, respectively). Although EDL did not recover from the value at 2.1%, infusion of nicorandil significantly shifted the end-diastolic length dose–response to isoflurane downwards (9.8 (0.2) to 9.9 (0.3) mm at 1.05% and 2.1% isoflurane, respectively). Regional systolic function assessed by $\%SS_{norm}$ and the slope of preload recruitable stroke work (Msw_{norm}) (fig. 3) were depressed in a dose-dependent manner with increasing isoflurane concentration. This was not altered by nicorandil. %SS decreased by approximately 30% between the lowest and highest concentrations of isoflurane; nicorandil had no significant effect. Msw_{norm} decreased from 100 to 60 (11)%, at 1.05% and 2.1% isoflurane, respectively; nicorandil had no significant effect.

Initial plasma concentration of nicorandil 30 min after bolus administration of 100 μg kg^{-1} and at the beginning of infusion of 25 μg kg^{-1} min^{-1} was 0.50 (0.04) mg litre^{-1}. Plasma concentrations increased during the study to reach 0.99 (0.04) mg litre^{-1} at the end of the experiment (table 3).

Discussion

Nicorandil, a novel K_{ATP} channel opener, has been shown to have profound effects on the cardiovascular system, producing alterations in preload and afterload by its vasodilatory effects on the venous and arterial circulations.[14] Clinical studies have shown that nicorandil significantly reduced left ventricular end-diastolic diameter and pressure by reduction in left ventricular filling.[15 16] Nicorandil also caused marked reductions in afterload, as shown by significant decreases in systolic pressure, associated with dilatation of peripheral large arteries resulting in decreased diastolic arterial pressure.[17] These actions of nicorandil can be attributed to its nitrate moiety and a selective increase in K^+ conductance by opening ATP-sensitive potassium (K_{ATP}) channels. This shortens the action potential, reducing trans-sarcolemmal Ca^{2+} influx.[18]

The effects of isoflurane on the cardiovascular system have been well documented, both clinically and experimentally. Haemodynamically, it has been well established that isoflurane produces dose-related decreases in arterial pressure (systolic, diastolic and mean), stroke volume and global indices of contractility, such as $+dP/dt$.[5 19–21] Regional indices of contractility such as systolic shortening and preload recruitable stroke work are also decreased in a dose-dependent manner.[5 22 23] The negative inotropic and vasodilatory actions of volatile anaesthetics such as isoflurane can be attributed to alterations in voltage-dependent slow calcium (Ca^{2+}) channel activity in the sarcolemmal membrane.[24] It has been shown that isoflurane causes depression of Ca^{2+} influx during membrane excitation and a reduction in sarcoplasmic reticulum Ca^{2+} release, resulting ultimately in less Ca^{2+} available for the contractile proteins.[25] However, recent studies[8 9] have shown that isoflurane-induced vasodilatation was antagonized by glibenclamide, an inhibitor of the K_{ATP} channel, suggesting that the vasodilatory action of isoflurane is mediated partly by K_{ATP} channels.

With such profound individual effects of nicorandil and isoflurane on systemic haemodynamics and cardiac function, the question must be raised as to whether there may be an additive action after combined administration.

Our results showed that increasing isoflurane concentrations, ranging from 1.05% to 2.1%, produced expected "typical" dose–responses: a decrease in heart rate, systolic pressure and cardiac output. Systolic contractility, as assessed by preload recruitable stroke work (PRSW), a load-independent index,[13] and systolic shortening, decreased in a dose-dependent manner. These results have been confirmed in similar experimental models.[22 23] Increases in isoflurane concentration produced no change in coronary flow. This is expected as isoflurane causes dose-related coronary vasodilatation, thus allowing flow to be maintained while diastolic arterial pressure is decreasing. Pagel and colleagues[21] found that isoflurane (1.25 MAC) increased coronary flow and reduced end-diastolic pressure and systemic vascular resistance when conscious and anaesthetized dogs were compared. Increasing the isoflurane concentration to 1.75 MAC did not change these variables further.

In the presence of nicorandil, we found that there were downward shifts in end-diastolic pressure (ns) and end-diastolic length dose–responses to isoflurane. This would suggest that a vasodilatory effect of nicorandil with isoflurane occurs in the venous circulation, leading to a reduction in preload. The heart rate dose–response to isoflurane shifted upwards in the presence of nicorandil, probably as a result of a reflex reaction to the decrease in systolic pressure. Although heart rate increased, cardiac output did not increase and therefore stroke volume must have decreased, possibly as a result of a postulated increase in venous capacitance. We showed also a slight downward shift in the systolic pressure dose–response to isoflurane in the presence of nicorandil. By studying nicorandil in conscious dogs, Humphrey and Schwende[26] showed that after 2 h of i.v. infusion, a nicorandil plasma concentration of 0.8 mg litre^{-1} correlated with a reduction in mean arterial pressure of 20 mm Hg and an increase in heart rate of 40 beat min^{-1}. For similar concentrations of nicorandil, during isoflurane anaesthesia, our results showed a reduction in systolic arterial pressure of 10 mm Hg at 1.05% and 17 mm Hg at 2.05% isoflurane, with an increase in heart rate of 10 beat min^{-1} and 5 beat min^{-1}, respectively.

Nicorandil is known to produce an increase in coronary flow via its vasodilatory action.[17, 27] In our study we found an upward shift in the coronary flow dose–response to isoflurane in the presence of nicorandil, confirming the coronary vasodilatory properties of this agent. As the coronary vasodilatation produced by isoflurane was enhanced by nicorandil, this suggests that either there is an additive effect on K_{ATP} channels or the two drugs are causing vasodilatation via different mechanisms. In patients with steal prone distribution of coronary lesions, the additive coronary dilator effect of both drugs may be deleterious by inducing coronary steal. Indeed coronary steal has been described with isoflurane[28] and with pinacidil, another K_{ATP} channel opener.[29]

The time constant of relaxation (tau) dose–response to isoflurane showed a downward shift in the presence of nicorandil. This index of isovolumic relaxation must be interpreted carefully; it is affected by changes in heart rate and loading conditions.[30, 31]

Infusion of nicorandil shifted the dP/dtmax dose–response to isoflurane. However, this global index of contractility is known to be affected by changes in loading status.[32] As mentioned previously, there appeared to be a decrease in preload with nicorandil; this could account for the decrease in dP/dtmax. Load-independent indices such as $M\text{sw}_{\text{norm}}$[13] did not change with addition of nicorandil. Other studies concur with the observation that nicorandil has no effect on contractility.[2] In patients with coronary artery disease, nicorandil 20 mg orally decreased mean arterial pressure and peripheral arterial resistance without changing left ventricular contractility.[33] However, in another study,[34] ventricular function assessed angiographically and by echocardiography improved after pacing-induced myocardial ischaemia. This improvement was related to the coronary vasodilator properties of nicorandil. Our study carried out in dogs without coronary stenosis showed no change in ventricular function (assessed by systolic shortening and by the load-independent index, PRSW) when continuous perfusion of nicorandil was added to isoflurane anaesthesia.

Plasma concentrations of nicorandil tended to increase during the experiment. The dose of nicorandil (100 μg kg^{-1} bolus, 25 μg kg^{-1} min^{-1} continuous infusion) used in this study has been used in similar animal models.[2] Nicorandil concentrations measured in our study were close to therapeutic blood concentrations measured clinically. In patients with congestive heart failure, a single dose of nicorandil 40 mg orally resulted in a concentration of 0.45 mg $litre^{-1}$.[35] In healthy subjects, therapeutic blood concentrations were in a similar range: a single dose of nicorandil 40 mg orally produced a maximum concentration of 0.49 (0.26) mg $litre^{-1}$.[36]

Our study was performed in an acute, anaesthetized, open chest preparation. Therefore, the haemodynamic effects of the drugs may have been affected by the acute surgical intervention. Only nine animals were included in the study and the within-animal comparison was performed without a crossover design because of the prolonged half-life of nicorandil and the possibility of carry-over effects. The duration of the study was long, and we cannot exclude the possible effects of deterioration of the preparation. However, previous studies in this department have shown that this model remains stable for at least 4 h after the start of data collection.

In summary, concurrent administration of isoflurane and nicorandil caused additional vaso/venodilatory effects in a canine preparation compared with isoflurane alone. However, ventricular function was unaffected by combined administration of both drugs. Therefore, the association of isoflurane and nicorandil appears to be safe. However, we would exercise caution when extrapolating results in acutely instrumented dogs to the clinical setting.

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REVIEW ARTICLE

Population based pharmacokinetic analysis: why do we need it; what is it; and what has it told us about anaesthetics?

P. M. C. Wright

To study the time course of drug effects in biological systems requires appreciation of drug disposition within the organism; the science of pharmacokinetics. We need also to appreciate how drug effects relate to their concentration in plasma and at the site of action; this is pharmacodynamics. For the specialty of anaesthesia, these two related disciplines have made it possible to understand how anaesthetic drugs can have rapid, profound effects which dissipate rapidly and predictably. Typically, in pharmacokinetics and pharmacodynamics, an empirical mathematical model is defined that describes drug effect time course after administration. That model can then be used mechanistically to predict the action of other doses. Thus, doses and treatment regimens can be manipulated to optimize the safe and effective use of drugs. This is the true use of pharmacokinetics and pharmacodynamics; determination of appropriate dosing regimens.[1]

If the mechanistic extrapolation of an empirical pharmacokinetic model developed from data collected in a subject or subjects is reasonable, then we can attempt to predict what will happen in a further subject. In truth, the next subject often does not match our prediction. Of course, we do not expect that all patients respond in a similar manner; there is something missing from the model, a factor to account for variation between patients. Intuitively, we also expect that predictions are more in error the more different is the patient from those that were studied originally (e.g. extreme age or disrupted physiology).[6] If we can model the variability between patients, we can predict the magnitude of the expected discrepancy between our predictions and the observations in the next subject. Further, if we can model variability which can be explained on the basis of physiological differences, then predictions are improved because the unexplained residual variation is reduced. As doctors, we treat patients who are sick and it is these patients who are most likely to have drug effects inconsistent with our predictions. Conventional pharmacokinetic models take little account of physiological or pathological variation, and fail to predict the changes in drug effects which would be of greatest interest. They fail to take account of the complexity of variation within the populations in whom the drugs are used and make only rudimentary attempts to explain or predict these variations. For the anaesthetist using drugs in the entire population, young and elderly, sick and healthy, the variability in the pharmacokinetic parameters and how this variation is predicted by physiological variables is more useful then knowledge of the precise structure of a pharmacokinetic model.

Population approaches to pharmacokinetic–pharmacodynamic modelling attempt to integrate the variability of the parameters of the pharmacokinetic model into the modelling process and provide tools to explain these variations on the basis of differing biological characteristics. Some population approaches are capable of quantifying determinants of drug concentration or effect in individual patients, but it is the integration into the modelling process of variability in the structural parameters between patients that differentiate population methods from other methods. This integration alters profoundly the nature and quantity of information that is required from each individual. Typically, with a population approach, the entire population studied is modelled together and there is no necessity to have sufficient information data from each individual to independently define a predictive model for that individual. Small amounts of data collected in a non-stringent manner from large populations of patients can be modelled successfully. Thus population pharmacokinetics provides a tool allowing us to learn more effectively what we need to know to administer drugs safely in the clinical environment; namely, the degree and source of variation in the determinants of drug action in the population.

Sample mean pharmacokinetic parameters of a group of individuals provide a crude "typical" population model but erroneous estimates of variability. While this might be considered a form of population method, for the purpose of this article this methodology will be called the traditional two-stage method. Only methods which attempt to improve on traditional two-stage estimates of both "typical" parameters and variability in those parameters will be called population methods.

Why is the population approach necessary for pharmacokinetic data?

Population approaches are a logical departure from traditional methods of describing variability within

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the population. With traditional approaches, a model is defined for each individual, the parameters of which describe the plasma concentration (or effect) over time; these individual structural parameters are then treated as variables and are summarized across individuals using statistical parameters (typically sample mean and sample standard deviation). This approach, while satisfactory under some circumstances, is flawed. To understand why, it is necessary to consider in considerable depth the nature of pharmacokinetic data and, in particular, to understand the differences between measured variables and descriptive parameters, and precise measurements and imprecise estimates. The traditional approach to the analysis of pharmacokinetic data gives less information than might be extracted from the available data because it treats imprecise estimated parameters as precise measured variables. Ultimately this prevents the development of more sophisticated models.

MEASUREMENTS, VARIABLES AND PARAMETERS

Biological variables (as the name implies) demonstrate variability between and within individuals. To fully characterize a biological variable within an individual or a population requires a measure of this variation and a measure of the typical magnitude of the variable itself. The measures used to perform these functions are statistical parameters (often the standard deviation and the mean). Frequently, the variable can be measured (with a defined degree of precision) but, because we cannot take every measurement or study every subject, the parameters (e.g. mean and standard deviation) that characterize that variable can only be estimated (the estimates are correctly termed the *sample* mean and *sample* standard deviation). If we take arterial pressure as an example of a variable that we might measure with a great deal of precision, across individuals (or across time in one individual), we create a sample of values; we can take the sample mean and sample standard deviation of this series as *estimates* of the true mean and true standard deviation (which we can never know). Estimates are different from measurements in their additional degree of imprecision (i.e. they differ from the "true" value by an unknown amount). We acknowledge the additional degree of imprecision which arises from the estimation procedure in the standard error of the estimate (or in the confidence interval). Almost certainly the estimate of the mean that we obtain is not the same as the true mean for the population, indeed it may be quite different.

When the variable which we wish to characterize is itself estimated rather than measured, we have another source of imprecision; the relative importance of the two sources of imprecision may be difficult to separate and may also be important. This is the case in pharmacokinetics. The measurement made (with a small, but more importantly, defined degree of imprecision) is, typically, the plasma concentration of a drug. Plasma concentrations are characterized using descriptive parameters (e.g. clearance) which are estimated (sometimes with considerable imprecision). These estimated structural parameters then become the "variables" which are characterized using statistical parameter estimates (i.e. sample mean and sample standard deviation). The precision of the estimate for an individual's structural pharmacokinetic parameters can itself be estimated (and expressed as the standard error) and may be quite different between two different individuals (one may have more or better quality data). With the traditional approach, when we characterize these parameters for a population (e.g. define the sample mean and sample standard deviation) we have no mechanism for passing on our knowledge of the different precisions for each individual. The imprecision resulting from estimation of the sample mean and sample standard deviation of the pharmacokinetic parameters is compounded by the (perhaps considerable) imprecision already present in the pharmacokinetic parameter estimations for each individual. These two sources of imprecision cannot subsequently be separated, and are interpreted as variation between subjects. Put succinctly, the two-stage procedure for the characterization of pharmacokinetic parameters in a population confounds the precision error in the estimation of an individual's structural pharmacokinetic parameters with the variability in those parameters between individuals.

Imprecision in the estimation of pharmacokinetic parameters for an individual may be greater than we might intuitively expect. This is because of covariance in the pharmacokinetic parameters. Taking a simple monoexponential decline, two parameters are necessary to describe such a pattern, one to describe the rate of decline and one to scale the initial concentration. In the many possible combinations of the two parameters which describe a decline similar to one observed, the two values are not independent, indeed they are highly interdependent. Consider the following experiment: on 10 separate occasions an identical dose of drug is administered to the same individual. On each occasion, plasma concentration data are obtained at identical times. Even if the underlying pharmacokinetic model is identical, we do not expect identical sets of plasma concentration data because each time the plasma concentration is measured there is a small error. When models are fitted to data thus obtained, a slightly different set of structural parameters emerges on each occasion. The data in figure 1 represent the results of simulating such an experiment. The underlying model has one compartment and data were simulated 10 times with random error coded into each plasma concentration. One-compartment models were then fitted to the data set by set, producing 10 sets of pharmacokinetic parameters. There is apparent variation in the estimations of volume of distribution and clearance, yet we know that the true parameter values of the underlying model were identical for each set of data. The apparent variability between administrations is actually a manifestation of imprecision in each parameter introduced by the estimation process. The variation seen in each parameter is mirrored by highly correlated variation in the other. Thus considerable imprecision in both parameters is consistent with relatively little variability in the predicted plasma concentration. If the 10 drug administrations had been to different individuals and the traditional approach to analysis had been used, the imprecision in estimation of, and covariation in, the estimated pharmacokinetic parameters would appear as inter-

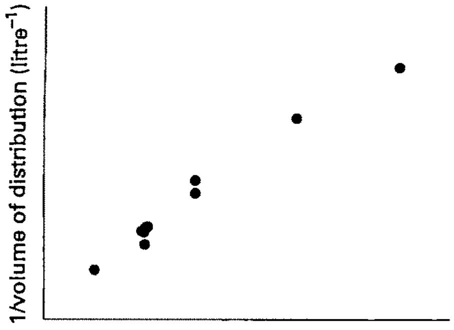

Figure 1 Point estimates of clearance and volume of distribution from a simulation of 10 identical administrations of a drug to the same individual. Because of error in the measurement of each plasma concentration, there is apparent variation in the point estimates, which is larger than might be expected because of covariation in the two parameters (see text).

individual variability in the pharmacokinetic parameters. Consequently, the investigator concludes (erroneously) that there is more variation in the pharmacokinetic parameters across the population than is really the case.

ESTIMATION AND WEIGHTING

We have examined the differences between measured variables and estimated parameters, and the problems that arise when we nest two estimation procedures, with statistical parameters (e.g. sample means) being estimated for structural pharmacokinetic parameters (e.g. clearance) which have themselves been estimated. Now we will examine the problems associated with estimation of structural descriptive parameters in more detail.

For a parameter describing the behaviour of a variable within a population of values (e.g. mean arterial pressure of a series of measurements) each individual measurement must by definition contribute some information. In the case of a sample mean this is an equal amount from each value for the variable. Implicitly we assume that each value is equally free of error and all values should be given equal weight in the determination of the parameter. If we examine our data before calculating a mean and notice that one value is unusually different from the rest, then we might exclude it as it is more likely to be in error. This is an example of weighting, where the unusual value has been down-weighted to contribute less information because it is more likely to be in error; in this case it is given zero weight.

In the same way when we describe a decline in plasma drug concentration (or change in drug effect) over time using a structural model, each value for drug concentration or effect contributes a certain amount of information to the estimate of the parameters. However, in this case the variable measured is not on the same scale as the parameter. The value to which the measured variable is approximating is the expected plasma concentration (the prediction). The prediction is analogous to the sample mean of the series of arterial pressures; each arterial pressure measured approximates the sample mean arterial pressure which predicts the true average arterial pressure. Unlike the sample mean arterial pressure (which has just one value in the same order of magnitude as the measurement) the predicted plasma concentration has many values. It is a function of the structural parameter and time and has many values which may span many orders of magnitude. Appropriate weighting of the observed values becomes a complex task.[52]

Estimating structural parameters which define a model describing a set of data always involves some variation of a least squares procedure (minimizing the sum of the squares of the difference between observed and expected values). The simple least squares procedure often will suffice but is known to produce biased parameter estimates with pharmacokinetic data. One reason for this is that plasma concentrations often decline in a polyexponential manner over time; they usually span many orders of magnitude. We expect the error of measurement to be larger for greater values. If we wish each value to contribute an equal amount of information to the final parameter estimation (a not unreasonable starting point) we must take account of the size of the expected error as a proportion of the size of the prediction, or larger values will contribute too much information. In addition, if visual inspection of the data indicates that a value is outside of what we would expect considering the rest of the data, then we might wish to reduce its influence (as we did with the outlier when calculating mean arterial pressure). We might down-weight it as a function of how far it lies from the expected value based on our knowledge of the other data points. The technical details of more sophisticated variations of ordinary least squares (e.g. extended least squares) are beyond the scope of this article; suffice to say that they can weight data optimally.[51 67 68] To weight appropriately requires that we make some assumptions regarding the distribution of the errors around the expected value of the observation[34] –this is what the sophisticated variations of least squares estimation permit. The most unbiased estimates are produced by procedures that allow the data to contribute to the assumptions made about the distribution of the errors. The more data there are, the better these assumptions are, and the more precise are the parameter estimations.

Practical advantages of the population approach

We have considered the problems that arise with an uncritical approach to pharmacokinetic analysis. If we simply fit each individual and then calculate sample mean pharmacokinetic parameters, we have no valid mechanism for weighting data from well conducted or problematical studies, or for weighting the parameters which come from studies with just a few or many data points. We also tend to conclude that there is more variability in the pharmacokinetic parameters across the population than is truly intrinsic to the data. As some of this apparent variability is consequent from imprecision in the individual parameter estimates or from covariation in those estimates within an individual, we draw erroneous conclusions as to the source and nature of any explanation for this variation. Probably because we are aware of these limitations, we confine pharmacokinetic analysis to well designed, well conducted studies so that the consequent misinformation is limited. Assume that there is an estimation method available which can fit data taking account appropriately of how "good" each data point is both within the data for that individual and weighting that individual's contribution according to how much information there is about him. Then we can perform pharmacokinetic, or pharmacodynamic, or indeed many other types of data modelling using data collected in very non-stringent ways.

With a finite resource available for the conduct of a pharmacokinetic study, we have a dichotomy of choice regarding the number of subjects that we study. We might study a few individuals and collect a great many blood samples from each individual, or we might study a great many patients but collect only a few samples from each one. Under the constraints of the traditional approach to pharmacokinetic analysis only the first approach is viable, and if the data are truly extensive within each individual then structural parameters may be estimated with precision and many of the problems previously identified are minimized. Both approaches have a place, but the second approach (only possible with population pharmacokinetic analysis), even assuming valid estimation procedures, gives superior information on the degree of variation and any explanation for this variation across the population. This is exactly the type of information that we defined as being valuable to the clinician. Further, if the method of analysis can weight data appropriately, perhaps we can model data collected not as part of a study but randomly collected in a very sparse manner in the course of treatment. Thus the population approach to pharmacokinetic analysis provides not only a tool to analyse pharmacokinetic data correctly, it can also facilitate experimental designs that are better able to yield the type of information that is useful.

Methods of population pharmacokinetic modelling

To understand the validity, advantages and disadvantages of the various methods for population modelling, we must first define some concepts for the structural and statistical parameters that make up the model, and the notation for these.

NOTATION

The following notations have become commonplace in the literature of population modelling.

Factors which predict response are notated as x and observed responses are notated as y. Individuals are known as a number I and the number of individuals studied is k (such that each individual is numbered so that $i=1, i=2, \ldots i=k$). Similarly observations within an individual are known as a number j and the number of observations within an individual is ni (such that each observation is numbered so that $j=1$, $j=2$, $\ldots j=ni$). With these notations we can consider the mathematical treatment of both individual models and population models. Below we will consider two types of models: *structural* models describe only a shape or curve (with no information on the distribution of random variation), and *data* models describe not only an underlying shape or curve, but also the nature of the distribution of the random variation expected (or observed) in the data.

Traditional structural model

Traditional structural modelling is applied to each individual's data in turn. The parameters emerging from this process apply only to that individual. The model may make no assumptions on the expected distribution of the residual errors about the predicted value for y. Put in terms of our notation the data take the form:

$$y_j = f(\theta, x_j)$$

where y_j=the jth observation of y in this individual; $f(\theta, x)$=parameterized curve describing an expected value for the response as a function of x for a parameter value θ–it is the predicted value of the response for this individual; and θ=parameter vector identifying the form of the relationship between x and y for this individual.

The values of any θ in the equation are altered so as to minimize the sum of the differences between the two sides of the equation for all values of y_j and hence the pharmacokinetic parameters are determined. The model recognizes only one individual at a time.

With this model there is no opportunity to weight the influence of a data point according to the expected distribution of the residual errors. An additional factor is required to transform this traditional model from a purely structural model for an individual to a data model for an individual, that is a statistical component describing the nature of the distribution of the random residual errors that can be used to define an expected degree of error for any particular prediction.

Individual data model

The corresponding data model for an individual has both structural and error distribution information. Put in terms of the described notation the data take the form:

$$y_j = f(\theta, x_j) + \varepsilon_j$$

where y_j =the jth observation of y in this individual; $f(\theta, x_j)$=parameterized curve describing an expected value for the response predicted by the value of x at the jth observation in this individual modified by the vector of the parameter θ; θ=parameter vector identifying the form of the relationship between x and y for this individual; and ε_j=zero-mean measurement error. Within this individual, all values of ε_j ($\varepsilon_1 \ldots\ldots \varepsilon_n$) come from a series which is normally distributed and has a mean of zero. How the variance of the epsilon varies with the magnitude of the expected observation may be coded into the modelling process. It might be assumed to be constant for all observations or it might be related to the size of the expected observation. The influence of data points can be weighted according to how far they lie from the expected value measured against this distribution.

The additional factor or factors which transform the structural model to a data model are ε variables. Epsilon (ε) has a new value for each observation but within an individual has a mean of zero and the values are normally distributed. The variance of epsilon is denoted by σ^2 (sigma squared) and the standard deviation by σ. The values of any σ are estimated as parameters of the model when they are fitted to the data. Thus the probability of any particular value of epsilon can be determined, and the appropriate weight of each observation assigned as part of the estimation process of the model.

Population data model

The corresponding data model for a population of individuals has both structural and error distribution information, and in addition it has information about the distribution of θ_i between the individuals in the model. Put in terms of the described notation the data take the form:

$$y_{ij} = f((\theta + \eta_i), x_{ij}) + \varepsilon_{ij}$$

where y_{ij} =the *j*th observation of y in the *i*th individual; $f((\theta + \eta_i), x_{ij})$=parameterized curve describing an expected value for the response predicted by the value of x at the *j*th observation in the *i*th individual modified by the vector of the parameter θ, itself modified by the factor η_i; θ=parameter vector identifying the form of the relationship between x and y for the typical individual; η_i=zero-mean variation in θ. The entire population has just one value for each structural parameter θ . Each individual's value for the structural parameter (θ_i) is determined by modifying θ by η_i. The population of values for η (one for each individual) has zero mean and is normally distributed. How the variance of the values of η varies according to the magnitude of the θ has to be assumed and coded; ε_{ij}=zero-mean measurement error. Within the *i*th individual, the value of ε_j is random, normally distributed and has a mean of zero. How the variance of epsilon varies with the magnitude of the expected observation must be assumed and coded into the modelling process. It might be assumed to be constant for all observations or it might be related to the size of the expected observation.

The additional factors in the population data model over the individual data model are the η factors. An η variable has a new value for each individual subject included in the data, but within a population has a mean of zero and the values are normally distributed. The variance of η is denoted by ω^2 (omega squared) and the standard deviation by ω. The value of any ω is determined as a parameter of the model.

Thus a population data model for a data set (assuming that there is more than one observation per individual and more than one individual) can be defined with the use of three types of parameters. Theta (θ) parameters are constant throughout the population, and consequently have just one value. Normally they are used as structural parameters of the model and their estimated values serve to define the structural model for a typical individual. They are also used to model for non-random variability between subjects (i.e. variation that can be explained, for example clearance is, on average, 30% less in one gender compared with the other). Eta (η) variables (the parameter in the model is their variance ω^2) have a new value for each individual but values are constant within an individual subject (or set of data intended to be treated as coming from one subject). They are constrained to have zero-mean and be normally distributed within a population. Typically they are used to code the random variability of structural parameters between individuals. Finally, epsilon (ε) variables (the parameter in the model is their variance σ^2) assume a new value for each observation, they are constrained to have zero mean and be normally distributed.

It does not follow that each θ must have a corresponding η (e.g. in a one-compartment model we might assume variability in clearance but not volume). Nor does it follow that there is only one σ parameter in a population model (e.g. we might assume that the variance of the expected measurement errors is mostly proportional to the magnitude of the expected error, but at low values becomes larger than this would predict, and this would require two σ parameters).

STATISTICAL METHODS

Many statistical methods have been propounded for estimation of population pharmacokinetic parameters and these are summarized below and in table 1. Whatever method is used many assumptions underlie the estimation process. Much care is required in the selection of models and parameterizations.[2 37 44]

Naive pooled data approach

If we focus attention entirely on the pharmacokinetic parameters which characterize the structural model and ignore completely the variance in these parameters when they are determined separately for each individual, then it might seem appropriate to pool all the data together as if they came from a single individual.[61] Such an approach is flawed in several respects as it ignores the dichotomy of source of variability in the response variable (plasma concentration). By the nature of the assumptions underlying the approach no information is available on individual profiles or parameters. Although standard errors can be calculated for the structural parameters estimated, measures of variability between individuals cannot be determined. Aspects of the pattern of the response which emerge from variation between individuals might easily but erroneously be interpreted as a more complex structural model than can be observed for any individual. Although the approach may be satisfactory when data are extensive for each individual and there is relatively minor inter-individual variability,[35] deviations from such conditions may result in erroneous results.[28 32] The approach is not recommended.[61]

Two-stage approaches

The traditional approach to pharmacokinetic analysis is to analyse subjects one by one, estimating parameters for each. Subsequently, the parameters describing each individual are combined in a summary measure (usually the arithmetic mean, but perhaps a geometric or weighted mean (e.g. weighted) according to the uncertainty associated with individual parameter estimates). The problems associated with this approach have been described previously.

In a population analysis, information on the structure of all individuals can input into the estimation of each individual's parameter estimates to "improve" these estimates. This is clearly not possible with a traditional two-stage approach, but some elaborations of this method attempt to implement this.[75] These include the "general two-stage" and "iterative two-stage"[53] procedures. They consist of multiple iterations through an algorithm, each iteration allowing all individuals' parameter estimates to modify the estimates for each individual. The details of these procedures are beyond the scope of this article, but until recently were suggested as being more reasonable than the next approach (non-linear mixed effects modelling) because of the latter's high computational overhead.[53] Even these procedures do not dispense with the necessity to obtain sufficient data from each individual so that their structural parameter values may be estimated. The same restrictions apply to the Bayes approach. With the Bayes approach, some prior but vague assumptions are made regarding the form of the mean population parameters and variability, and then information from each individual is used iteratively to adjust the assumptions. The Bayes approach has the advantage that it weights the contribution of each individual to the estimation of population structural parameters appropriately according to the amount of information available for each.

Non-linear mixed effects modelling

This is a procedure introduced by Sheiner and Beal in 1979.[69] The acronym NONMEM has become a common way to refer to this method, but it also refers to a proprietary computer package provided by a group headed by the same two individuals. The computer program NONMEM is not the only one now available for this type of analysis. The technicalities of the NONMEM approach are beyond the scope of this article[5]; essentially NONMEM is a full implementation of the population data model described above. All data from all individuals are fit together with information about the identity of individuals. Assumptions must be made regarding the form of the variation in each parameter between individuals and regarding the distribution of measurement errors. The form of each individual's concentration (or effect) profile is assumed to be similar to the "population" profile. Individual parameter values for some (not necessarily all) of the structural parameters are assumed to vary around the mean "population value" by a normal (or function of normal) fashion. Individual observations are assumed to vary around the predicted value in a normal (or function of normal) fashion and the values of the θ, ω and σ are estimated.

The NONMEM approach uses extended least squares in its minimization algorithm and weights values and individuals appropriately. It can provide valid structural parameter estimates for a "typical" individual on as little as two or three data points per individual. It has the advantage, when combined with empirical Bayes forecasting, of not requiring sufficient data from each individual to estimate their structural parameters independently.[26 48 77] It also has the advantage that a full variance–covariance matrix for all parameter estimations is estimated. Consequently the precision (standard error, or confidence interval) of each parameter estimation can be determined. The "true" variability of each structural parameter across the population is provided,[20] unconfounded by variation arising from assay error within an individual.

The main disadvantage of the method arises from the computational complexities involved in the estimation process. These are essentially two-fold. First, many assumptions must be made about the form of the structural model and the form of inter-individual variation between parameters. If the model is poorly or excessively parameterized (for

Table 1 Methods for analysis of pharmacokinetic data obtained from a population of individuals. *Two-stage analysis is included in the table for completeness. Average population pharmacokinetic parameters can be obtained only in specific circumstances and estimates of variability may be poor. This review reserves the term population methods for methods which attempt to improve on two-stage analysis

	Two-stage analysis*	Naive pooled analysis	Mixed effects analysis
Nature of the analysis	A descriptive structural model is fit to each individual. As a second stage the parameters of the structural models are summarized statistically	A descriptive structural model is fit to data from all individuals as if they were one individual	A descriptive structural model is fit to the data from all individuals. Variation between and within individuals is explained using statistical parameters within the modelling process
Study design requirements	Stringent study design necessary	Stringent study design not essential	Stringent or non-stringent study design Suitable for observational data
Amount of data required	Extensive within each individual	Extensive or sparse within individuals	Extensive or sparse within individuals. There may be uneven amounts of data from different individuals
Quality of parameter estimates for a typical individual			
Structural	Available if study design stringent	Available if study design stringent, but data from different individuals weighted incorrectly	Available
Variability	Only available as a separate statistical analysis. Variability in structural parameters may be overestimated	Not available	Available
Individual estimates	Available	Not available	Available (via empirical Bayes approach)
Modelled variation	Not available, except as part of the separate statistical analysis	Possible (unguided)	Available (guided)

instance attempting to fit a three-compartment model to data that truly support only two compartments), the method may frequently run into numerical difficulties. Second is the "overhead" of computational time required for the method. Even relatively modest problems may take hours of computation for a single estimation, and when data are extensive within each individual then it is not uncommon for a single estimation to take several days. As computers become faster and more powerful this is becoming less of a consideration. For many problems the non-linear mixed effects approach provides superior solutions compared with the two other approaches.[64–66]

Non-linear mixed effects modelling is frequently combined with a derivation of Bayesian techniques–empirical Bayes forecasting–to determine individual structural parameter estimates when the amount of data available for each individual would not have been sufficient to estimate their structural parameters in isolation. Non-linear mixed effects modelling provides sound estimates of the population structural parameters and their variance–covariance. When these are available, empirical Bayes forecasting allows an individual's structural parameters to be predicted even when very little data are present for that individual.[62 63] These individual estimates for structural parameters can then be used to guide the determination of any "explainable" variation.[22 44] Thus individual values for clearance, for example, may be plotted against a physiological covariate (e.g. weight) to gain a graphical insight into whether clearance varies systematically with weight.

What has the population approach told us about anaesthetic drugs?

Although appropriate methods of dealing statistically with pharmacokinetic and pharmacodynamic data have been available for about two decades they have only slowly reached acceptance and widespread use. No doubt this was in part a function of the computationally intense nature of the required analyses, which kept these techniques as a specialist tool for much of that time. It is only in the 1990s that population pharmacokinetic analysis has appeared more than sporadically in the methodology of studies of anaesthesia drugs and techniques. The review which follows concentrates on studies which use full data models to explain drug time course in entire populations; and on studies which examine the utility of such models. Studies of anaesthetic drugs and techniques which use mixed effects modelling or naive pooled data analysis are also summarized in table 2.

OPIOID DRUGS

Probably because of the difficulty in monitoring their effects, opioid drugs have received much attention from population pharmacokineticists. The effect of an anaesthetic or neuromuscular blocking agent can be observed during an operation using simple, widely available methods. However, there is no simple test to monitor the effects of opioids in anaesthetized patients. Inadequate dosing may result in intraoperative stress or postoperative pain while an overdose may compromise respiration. A predictive model may allow these undesirable outcomes to be avoided more frequently. By its very nature, mixed effects modelling is well suited to predictive (mechanistic) modelling as its "typical" parameter set is not necessarily a geometric mean of individual parameters but is probably more representative of a typical individual. In addition, a variance–covariance matrix is estimated and allows individualization of parameters via Bayesian forecasting. In predictive modelling, variability in the model parameters can often be reduced by modelling parameters as functions of physiological covariates (e.g. gender or weight), hence improving the accuracy of the prediction for each individual. A difficulty arises because of the number of possible candidate parameters and covariates to test in fresh models, especially given the computational overhead of mixed effects modelling. Some general schemes to ensure a systematic approach and thereby minimize the resources committed to each problem have been proposed.[44]

Alfentanil

Of all of the anaesthetic drugs, alfentanil was the first to receive the intense scrutiny of population pharmacokinetic methods. Using a randomly selected subset representing half of the plasma concentration data points from four studies,[7 11 29 57] Maitre and colleagues built a population pharmacokinetic model using non-linear mixed effects modelling.[43] The article was accompanied by an editorial[27] and may represent the first mainstream introduction of population methods into anaesthesia research. The group investigated the influence of several physiological covariates on the structural parameters of the model in an attempt to explain some of the inter-individual variability in the parameters of a three-compartment model. They noted that differences between patients in observed drug disposition could be explained by allowing variability in just two structural parameters (clearance and central volume of distribution). Had they had more data they might have been able to define degrees of variability in more of the pharmacokinetic parameters. The authors were able to explain some of the variability observed on the basis of physiological covariates (e.g. they found that clearance was not influenced by age up to 40 yr, then declined in a linear manner). When all explainable variability was modelled, the remaining degree of variability was small (coefficients of variation of 48% and 33% for clearance and central volume of distribution, respectively), and there was a considerable degree of correlation between these parameters. Hence the study illustrates effectively some practical advantages of the population approach. Had the authors used traditional two-stage data analysis they would have had no option but to report variability in all pharmacokinetic parameters, probably at a much greater magnitude than is truly the case. The authors validated their model against plasma concentration data not used in the analysis and produced a confidence range of prediction for plasma concentration in each individual.

There are some limitations to the use of information generated by this analysis (which were acknowledged by the authors). Principle among these is that the model provides only a predicted range of plasma concentrations for an individual (not drug effect which is the variable of true interest). Thus plasma concentrations have no real value unless compared against some prior knowledge of the magnitude of plasma concentration associated with desired effects. Using data from a previous study[3 4] designed to evaluate the range of plasma concentrations of alfentanil associated with clinical effects, the group went on the evaluate the predictive performance of their "typical" population pharmacokinetic model.[59] They found that their model predicted plasma concentrations with a small mean bias (7.9% under prediction) and a mean absolute error of 22%. They considered that these results indicated that their model was sufficiently robust for clinical use.

That further individuals given a dose of drug to achieve a given response will demonstrate a range of responses is intrinsic to any pharmacokinetic model. Thus if the population pharmacokinetic model can be "modified" for an individual, predictions are improved for that individual. The same research group carried out a further study on the same data designed to investigate methods of individualizing the pharmacokinetic model used for dosing. With prior knowledge of the behaviour of the population (both "typical" behaviour and variability), relatively little information is required using empirical Bayesian techniques to estimate the pharmacokinetic parameters of a new individual.[62] Using a single plasma concentration value from each individual the group applied this Bayesian forecasting to produce individualized pharmacokinetic models and demonstrated that the mean absolute error could be reduced to 13.8% using a single plasma concentration from each individual to "modify" the structural model for that individual.[42] Adding additional data points did not further improve predictions. Unfortunately, to use such a technique in clinical practice would require a very rapid technique to measure the drug concentration, something that is not yet available.

The predictive performance of Maitre's population model of alfentanil[43] has been evaluated prospectively at other centres. Raemer's group evaluated the performance of the Maitre population model and another pharmacokinetic model of alfentanil derived by Scott and Stanski[58] using traditional two-stage

Table 2 Studies which use "population" analysis methods to evaluate anaesthetic agents or techniques. The table is restricted to studies using analysis methods which attempt to "improve" upon two-stage mean parameter estimates for a typical individual. *Data: extensive=sufficient from all individuals to fit a model to that individual; sparse=insufficient from some individuals to fit satisfactory individual model. †Study design: stringent=tight control over dosing, number and timing of blood samples, individuals all treated similarly; semi-stringent=some variation in dosing or sampling regimen permitted between individuals or data taken from more than one study; observational=wide variations in dosing or sampling regimen between individual subjects. ‡Data analysis: TS=two-stage analysis; NPD=naive pooled data analysis; MEM=mixed effects modelling; (cov)=with modelled covariate effects; NONCOMP=non-compartmental analysis

Drug	First author (reference No.)	Data*, design†, No. of subjects	Data analysis‡	Model evaluation or comparison group	Patient groups
Alfentanil	Maitre[43]	Extensive, non-stringent, 45	MEM (cov)	Prospectively (28, 32, 53)	Adult patients
	Fiset[18]	Extensive, stringent, 14	NPD	Cross validation	Children having cardiac surgery
Remifentanil	Egan[16]	Extensive, stringent, 10	TS, NPD, MEM	Compares analysis methods	Male volunteers
	Westmoreland[81]	Extensive, stringent, 24	TS, MEM	Compares analysis methods	Adult patients
	Egan[17]	Extensive, stringent, 10	MEM	Compares remi. with alf.	Male volunteers
	Minto[44]	Extensive, semi-stringent, 65	MEM (cov)	No	Adult patients
Fentanyl	Shafer[59]	Extensive, semi-stringent, 21	NPD	Retrospectively	Adult patients
	Ginsberg[24]	Sparse, semi-stringent, 20	MEM (cov)	Retrospectively	Children
Sufentanil	Gepts[23]	Extensive, stringent, 23	TS, NPD, MEM	Evaluates linearity	Adult patients
Rocuronium	Szenohradsky[76]	Extensive, stringent, 10+10	MEM	Compares with normals	Adults with renal failure
	Magorian[38]	Extensive, stringent, 10	MEM	Compares with normals	Adults with liver disease
	Larijani[36]	Extensive, stringent, 10+11	MEM	Compares with no isoflurane	Adults receiving isoflurane
	Vuksanaj[80]	Sparse, stringent, 20	NPD, MEM (cov)	Not evaluated	Children
	Fisher[19]	Extensive, stringent, 20	MEM (cov)	Examines liver transplant	Adult patients
Cisatracurium	Sorooshian[73]	Sparse, semi-stringent, 31+33	MEM (cov)	Compares with adults	Elderly patients
	Schmith[55]	Sparse, observational, 241	MEM (cov)	Not evaluated	Adult patients
	Smith[70]	Extensive, semi-stringent, 20	MEM (cov)	Compares isomers	Adult patients
Propofol	Kataria[53]	Extensive, semi-stringent, 53	TS, NPD, MEM (cov)	Compares analysis methods	Children
	Murat[49]	Extensive, stringent, 12	TS, MEM, NONCOMP	Compares analysis methods	Burned small children
	Frenkel[21]	Extensive, observational, 18	MEM	Not evaluated	Intensive care patients
Midazolam	Maitre[40]	Sparse, semi stringent, 64	MEM (cov)	Not evaluated	Surgical patients and volunteers
	Burtin[10]	Sparse, observational, 187	MEM (cov)	Not evaluated	Critically ill neonates
Thiopental	Stanski[74]	Extensive, semi-stringent, 64	MEM (cov)	Examines the effect of age	Healthy adults
ORG 21465	Sneyd[71 72]	Extensive, stringent, 10	MEM (cov)	Not evaluated	Healthy male volunteers
Spinal block	Schnider[56]	Sparse, observational, 96	MEM (cov)	Not evaluated	Healthy surgical patients

analysis.[54] Contrary to expectations, this study found that the model of Scott predicted plasma concentrations in two disparate populations substantially better than Maitre's model (which under predicted plasma concentrations of alfentanil). The authors discussed a variety of explanations for this unexpected finding. Jenstrup and co-workers evaluated the Maitre model in middle-aged females and also found systematic under prediction of plasma alfentanil concentration.[35] Similarly, Barvais and colleagues[5a] administered drugs to patients undergoing cardiac surgery according to the Maitre model for the middle aged and the model of Helmers and colleagues[29] (derived using the traditional two-stage approach) for elderly patients. They retrospectively evaluated the predictive performance of these two models and several other alfentanil models taken from the literature. All models under predicted the observed plasma concentrations with the exception of the model of Scott and Stanski.[58] The importance of prospective evaluation of pharmacokinetic models has been acknowledged by the Maitre group.[79]

More recently, two further population models of alfentanil have been published. One is derived from data collected in critically ill patients receiving these drugs for sedation in the intensive care unit.[21] In principle, the long duration of drug administration sampled during this study may be advantageous in providing data that allow a very predictive model. However, this model has not been evaluated at present. Interestingly, this model has a clearance for alfentanil which is similar to that of the Maitre model suggesting that it also might under predict alfentanil plasma concentrations in prospective evaluations. Another model, also as yet not evaluated, is derived from data in surgical patients and also has a value for clearance similar to the Maitre model.[17]

Alfentanil pharmacokinetics have been investigated in children using naive pooled data analysis. Fiset and colleagues[18] used a model with its parameters estimated using a traditional two-stage approach from data taken from healthy children[25] to calculate infusion doses for 14 further children undergoing cardiopulmonary bypass. The authors used naive pooled data analysis to define new models of varying complexity. The median absolute error of the two-stage model used to compute the dose schedule was 33% but was in the range 18–20% for the naive pooled data models. However, given that these models were estimated from the same data as they were evaluated against, we cannot infer that the naive pooled data method is preferred over the two-stage method. In these studies, very extensive data were available for all individuals so that most pharmacokinetic methods would be expected to perform well.

Remifentanil

Remifentanil is an opioid drug which, because of its disposition in the body, is much more predictable than all other opioids. It is cleared very rapidly so that recovery takes place soon after infusion is discontinued, irrespective of the dose or duration. In this case we desire a pharmacokinetic model more for explanatory than predictive purposes, and population pharmacokinetics has less to offer. Nevertheless, population pharmacokinetic techniques have been used widely in its evaluation, in part because it is a drug which has recently been developed. Two early studies used traditional two-stage and mixed effects modelling to analyse the same data,[16 81] and one of these also used naive pooled data analysis.[16] The data in both of these studies came from small groups of homogenous individuals and consisted of an extensive data set for each individual. Under these circumstances, where the requirements necessary for individual pharmacokinetic analysis are met, and inter-individual variation is expected to be modest, all procedures are expected to perform well. Indeed in both studies all methods gave similar average structural models for remifentanil. The other possible advantage in using mixed effects modelling is its ability to estimate a valid variance–covariance matrix. However, in these particular circumstances, mixed effects modelling gives little advantage because few subjects were studied and variability would inevitably be poorly estimated whatever analysis method is used. Similarly, in a study comparing remifentanil with alfentanil,[17] extensive data were obtained from small groups of individuals; mixed effects modelling was used but probably gave similar results to any other method that might have been chosen. In a study examining differences in response to remifentanil in subjects with liver disease,[12] extensive data were collected from small numbers of subjects and the authors successfully used two-stage pharmacokinetic analysis.

More recently, Minto and colleagues have presented a population pharmacokinetic analysis of remifentanil that depends more critically on the use of mixed effects modelling.[46] This analysis includes extensive data for 65 individuals, some of whom appeared in earlier studies,[16 17] and goes further than many earlier population pharmacokinetic studies of opioids in that a population pharmacodynamic model of spectral edge frequency was also developed. Individual pharmacokinetic analysis was carried out on all 65 subjects, a two-compartment model could be fitted to half of the subjects; the remainder required a three-compartment model. The authors wished to build a covariate model to explain as much inter-individual variation as possible; this is difficult if the structure of the pharmacokinetic model differs between individuals. It is likely that the individuals in whom the data could support only a two-compartment model would have supported a three-compartment model had more or better quality data been available. In this setting, mixed effects modelling of a three-compartment model to all data combined with Bayesian prediction of individual parameter values makes this process possible. Among a host of covariate effects the authors demonstrated convincingly that clearance, central volume of distribution and biophase equilibration all decrease substantially with age while tissue sensitivity to remifentanil increases with age. In an accompanying article, the authors used their model to determine, given the intrinsic predictability of remifentanil, whether any covariate effects that they were able to model would have a clinical impact.[47]

Other opioids

Most available opioids were already well established in clinical practice before population pharmacokinetic methods began permeating the anaesthesia research community. Consequently there are only sporadic studies of other opioids which use these techniques. Shafer and colleagues[59] used two pharmacokinetic parameter sets[45,58] to program a syringe controller and gave fentanyl to 21 adult patients using one or other of the sets, aiming to produce rapidly stable plasma concentrations. They collected multiple plasma concentrations from each of the patients and analysed these to estimate a new pharmacokinetic parameter set. To achieve this, they first attempted a two-stage approach, but had difficulty because the duration of infusion influenced the parameter estimates to a great extent because of the differing quantity of data. They recognized this problem and used naive pooled data analysis (which would now be recognized as an imperfect solution because it does not weight the input of the individual's contribution to the fit according to the quality of their data). The ability of their parameter set to predict fentanyl concentrations of four previous studies[31,45,58,78] varied from slightly worse to better than the parameters derived by the original investigators using two-stage analysis. Their methodology was rather less naive when they performed a similar study in children and developed a new pharmacokinetic parameter set in children using mixed effects modelling which included a considerable number of covariate effects.[24]

Demonstration of linearity (i.e. independence of concentration) in the pharmacokinetics of a drug is of great importance if models are to be used in determining doses and predicting concentrations. This represents a potentially difficult problem in pharmacokinetic research as giving a larger dose typically results in a longer duration of detectable plasma concentration. There may be more information available after the greater dose, and later, slower half-lives may be detectable. Thus a drug which truly has linear pharmacokinetics may appear to be non-linear. Mixed effects modelling is potentially a solution to this problem. Gepts and colleagues have performed such an analysis with sufentanil. They administered multiple dose levels to surgical patients and subsequently analysed plasma sufentanil data using naive pooled, two-stage, and mixed effects modelling.[25] Analysis of linearity was confined to a very sophisticated two-stage analysis however, and although mixed effects and naive pooled models are presented they did not include data from smaller doses, these having been deleted as potentially misleading. The authors conclude that the "best" model emerged from the two-stage analysis. However, if all of the data had been included for all of the analyses, the mixed effects model might have emerged as 'best' as it is theoretically capable of dealing appropriately with censored data from some subjects.

NEUROMUSCULAR BLOCKING DRUGS

As with opioid drugs, neuromuscular blocking agents have been subject to population pharmacokinetic analysis only in recent years: consequently there is a predominance of literature concerning recently developed drugs. A population pharmacokinetic evaluation was coordinated into the clinical development program of cisatracrium.[55] As it models pharmacokinetic and pharmacodynamic data from several hundred patients, it may prove to have considerable predictive value. However, at present it has not been evaluated. A similar project was undertaken during the development of ORG 9487 but has yet to appear in the literature. With neuromuscular blocking agents there has been less emphasis on the predictive performance of parameter sets (perhaps because the effects of neuromuscular blocking agents are easily measured and monitored). Pharmacokinetic modelling can still be useful in explaining differences observed in drug effects between patient groups. When the most likely explanation for an observed difference in effect is determined, the model can be used to predict differences with other dose regimens. Population modelling and mixed effects modelling in particular have a place in providing a sound data model which allows for hypothesis testing. Thus mixed effects modelling can provide a tool to determine the most likely of several candidate explanations for differences between subsets of individual subjects.[44,82]

Rocuronium

Four recent studies have used population approaches to determine the explanation for the time course differences of rocuronium in specific subsets of patients. Szenohradszky and colleagues studied 10 healthy surgical patients and 10 patients with end-stage renal failure receiving rocuronium. They used mixed effects modelling to determine which parameters of a three-compartment model varied between groups. They determined that clearance was unaltered by renal failure but that distribution volumes were increased. The authors did not carry out a two-stage analysis which, given the extensive sampling and small numbers of patients, may have given similar results.[76] More recently the same group have reported a similar study comparing healthy patients and those with severe liver disease.[38] They found that clearance of rocuronium was not altered in liver disease but distributional volumes were increased.[38] They went on to use mixed effect modelling techniques to examine the degree to which disposition of rocuronium altered during the course of liver transplantation and found that clearance of rocuronium correlated negatively with duration of warm ischaemia.[19] Larijani and colleagues compared the dose requirements and pharmacokinetics of rocuronium in the presence or absence of isoflurane; parameter differences between the groups were determined using mixed effects modelling.[36] Clearance of rocuronium was increased in the presence of isoflurane, explaining why infusion dose requirements were similar, despite the expected potentiation of rocuronium by isoflurane.

Vuksanaj and Fisher examined the pharmacokinetics of rocuronium in children aged 4–11 yr.[80] To minimize the volume of blood required, they sampled each child on four occasions. With such a study design only naive pooled and mixed effects modelling are possible, and individual pharmacokinetics can only be forecast using mixed effects modelling and empirical Bayesian techniques. The authors carried out naive pooled and mixed effects analyses to investigate the influence of covariates on pharmacokinetic parameters. The two techniques gave similar results (i.e. all parameters are best scaled by weight except clearance which is best described by a constant and a constant × weight).

Cisatracurium

The development of cisatracurium has included studies analysed using both traditional two-stage pharmacokinetic modeling[8 15 50] and mixed effects modelling.[70 73] Many of the clinical studies conducted during the later stages of the clinical evaluation of cisatracurium involved the collection of a limited number of blood samples from each individual. Such data are suitable for population based pharmacokinetic analyses; two such analyses appear in the published literature. One examines only the effect of age[73]; the other attempts a general predictive model of concentration and effect.[55] Two studies examined the time course of the effect of cisatracurium and its pharmacokinetics in elderly compared with young adult patients; one used extensive sampling in limited numbers of subjects and traditional two-stage analysis,[50] the other used sparse sampling in a much larger sample of patients and mixed effects modelling.[73] The two studies reported similar "typical" pharmacokinetic model parameters for the two patient groups and concluded similarly that volume of distribution was increased in the elderly. However, the fact that a larger number of patients were studied for the sparse sampling/mixed effects analysis study means that its estimates for inter-individual variability probably are more representative. The mixed effects analysis presents, in addition, a population pharmacodynamic model which is more informative regarding the explanation behind any differences in the time course of the drug in young and elderly patients. More recently, another study has evaluated the infusion pharmacokinetics of cisatracurium (and two other isomers present in atracurium) using mixed effects modelling.[70] Relatively few patients were studied but a negative influence of age on clearance still appeared as a significant covariate effect.

ANAESTHETIC AGENTS

As most anaesthetic agents and sedatives are well established in clinical practice, population pharmacokinetic techniques have been used only sporadically to elucidate residual problems.

Propofol

Recent pharmacokinetic research on propofol has concentrated on children and, not surprisingly, population modelling has been used in these studies. Two groups have studied the pharmacokinetics of propofol in children.[35 49] Both collected extensive samples from limited numbers of children and both determined that in these circumstances naive pooled data analysis, mixed effects modelling and traditional two-stage analysis gave similar results. In the circumstances of extensive sampling and a well conducted study, these findings are expected. Both determined a three-compartment model with clearance and volumes related to weight. If the pharmacokinetics of propofol in neonates are to be determined, a population approach may be necessary.

Frenkel and colleagues have produced a population pharmacokinetic model of propofol from data obtained during long-term infusion in the ITU in 18 patients.[21] Sampling was extensive and in this limited number of patients it is doubtful if a population approach gave any additional information.

Midazolam

Midazolam has a pharmacokinetic profile which makes recovery after its use difficult to predict, particularly in sick patients.[41] Maitre and co-workers developed a population data model of the effects of midazolam from data in 64 subjects. They used Bayesian forecasting to provide individual parameter estimates and used these to guide the modelling of covariate effects.[40] These methodologies have now become routine and are built in to current versions of NONMEM.

Another group has subsequently taken a fresh look at the pharmacokinetics of midazolam in neonates using sparse sampling and mixed effects analysis with covariate effect modelling.[10] Because of the limitations imposed by the small blood volume in neonates, the authors sampled the plasma infrequently; analysis of these data is only possible using population pharmacokinetic techniques. Despite their finding that clearance of midazolam was highly correlated with birth weight and prematurity, even when all covariate effects were modelled, residual variability was still considerable.

Aarons, Mandema and Danhof[1] also examined the problem of predicting midazolam effect from a different perspective. They performed a study in rats and demonstrated that individual pharmacodynamic models (which generally need *a priori* definition of the plasma concentration) built on a "typical" pharmacokinetic profile have a predictive performance inferior to those built on an individual pharmacokinetic profile. They demonstrated further that an individualized pharmacokinetic model (using just one plasma concentration and Bayesian forecasting to modify the "typical" population profile) was indistinguishable from a full individual model as a base for pharmacodynamic modelling.[1]

Thiopental

Applying pharmacokinetics to explain observed effects with thiopental is fraught with difficulty because of its extremely rapid onset of action. Much of the effect appears very shortly after administration. Compartmental models often make the assumption that drugs mix instantaneously with the volumes into which they are administered. This is not true and this aberrant assumption becomes important when an accurate description is required of the early arterial concentrations of the drug as a base for pharmacodynamic modelling. A group led by Stanski examined the effect of age on the disposition of thiopental using both two-stage techniques and mixed effects modelling. In the first study,[30] using two-stage analysis, they determined that the initial volume of distribution of thiopental is reduced in the elderly and this accounts for the reduced dose requirements in the elderly. In their second study,[74] using mixed effect modelling they were able to include more subjects (who had incomplete arterial concentration data and could not be studied using two-stage analysis) and they excluded patients who had received a bolus (rather than rapid infusion) of thiopental because of the difficulties outlined above. This study preferred a reduced rate of early distribution in the elderly over reduced central volume of distribution as the explanation for the reduced dose requirements. Probably the explanation proposed by the later study for reduced dose requirements in the elderly is more likely given the greater validity of the methods used. In the preceding case, mixed effects modelling was not a prerequisite for the more valid explanation. However, because it allowed inclusion of more subjects, and allowed valid comparison of which parameters were more likely to vary with age, it was instrumental in the discovery process. Of note is the fact that both methodologies correctly identified pharmacokinetic factors as the explanation for reduced thiopental dose requirements in the elderly and both determined that the young and elderly were similar in brain sensitivity and equilibration rate between plasma and brain.

Other anaesthetic agents

Population pharmacokinetic techniques are becoming integrated into the drug development process. Sneyd's group have used mixed effects modelling to characterize the pharmacokinetics and dynamics of a candidate i.v. anaesthetic from data obtained during its first few administrations to volunteers.[71 72] In both these studies extensive plasma concentration data were available from each individual and two-stage analysis would have been possible, but mixed effects modelling demonstrated that the effects of the drug could be explained in each individual with little variation of the model between individuals. As predictability is important in an anaesthetic, this information is useful in deciding if similar compounds are worth studying. Similarly, in two studies, the pharmacokinetics of dexmedetomidine were studied in 10 volunteers[14] and a population model developed to allow inclusion of covariates into the model.[13] The predictive performance of this model was tested on a further six subjects.[13] Both examples represent "pilot" use of population pharmacokinetics as estimates of variability across the population (one of the prime advantages of these techniques) are estimated only with poor precision with such few subjects.

OTHER ANAESTHETIC TECHNIQUES

Mixed effects modelling provides an ability to analyse data collected in a non-stringent observational way. This aspect of population data modelling has been little applied in the anaesthesia literature to date. However, given the ability of mixed effects modelling to explain variation and thereby possibly provide more powerful statistical testing, this may be an important application in the future. Two recent studies in the anaesthesia literature have presented work which takes advantage of this aspect of mixed effects modelling.

Shangraw and Fisher examined the disposition of dichloroacetate (DCA) during liver transplantation.[60] The drug was administered on two occasions by a short infusion and after each infusion, extensive blood samples were obtained. However, because the authors wished to investigate potential changes in DCA associated with removing the diseased liver and transplanting a donor organ, there were three sets of pharmacokinetic parameters, during three phases (paleohepatic, anhepatic and neohepatic) associated with a variable number of samples after two infusions. There would have been insufficient data during some of these phases to fit independent models with acceptable precision. Mixed effects modelling was used successfully by the authors to demonstrate that clearance of DCA approaches zero during the anhepatic phase.

Much of my review has presented population data modelling as a pharmacokinetic modelling technique. The majority of its use has been in pharmacokinetics but population data modelling can be applied to many non-pharmacokinetic data sets. The prerequisites for a population data model are that the data have a structure which can be expressed mathematically; there should be more than one data point per individual; data should be obtained from a variety of individuals; and measurement errors should be expected. Just such an analysis has been carried out recently to model the time course of spinal anaesthesia in a population.[56] Data were collected in a relatively sparse, non-stringent manner for another purpose. After spinal injection, the dermatomal level of spinal block was measured 4–10 times in each of 96 patients. A population data model was fitted to these data and covariate effects sought and modelled. Among the effects modelled (and therefore predicted by the model) was that onset time for block increased with height and decreased with weight. Thus a tall thin person is predicted to have the longest onset time for spinal block and a short heavy person the shortest time. By far the most important aspect of this study is its application of population data modelling techniques to model effect in the absence of drug concentration information (a technique only recently applied to single subjects).[9] Many of the problems currently addressed by clinical research in anaesthesia are potential candidates for this type of analysis.

In this article, I have considered how population pharmacokinetics is concerned with the provision of the most valid possible estimates for the behaviour of drugs in "typical" individuals. As the most obvious purpose for such information is to predict accurately the effect of drugs in new individuals, it is not surprising that tools have been developed to explain variation in drug behaviour on the basis of observable covariates; I have considered these also. I have examined how the methods which have emerged to analyse data addressing these issues have also provided some additional use in allowing valid analysis of observational data. I have examined the value of these methods to anaesthetic research; what information has been provided that we might otherwise not know. Finally, I have examined how the techniques involved may be used to allow the valid analysis of non-pharmacokinetic complex data sets.

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British Journal of Anaesthesia 1998; **80**: 502–503

SHORT COMMUNICATIONS

Leucocyte distribution during sevoflurane anaesthesia

H. MORISAKI, Y. AOYAMA, M. SHIMADA, R. OCHIAI AND J. TAKEDA

Summary

We have examined if sevoflurane anaesthesia *per se* modified the number of circulating leucocytes in humans. Fifty-nine patients undergoing elective surgery were anaesthetized with sevoflurane in oxygen. The inhaled concentration was increased gradually to 5% and maintained for 20 min. Arterial blood samples were obtained before induction of anaesthesia and at 20 min. While the total number of leucocytes remained constant, circulating neutrophils decreased (mean 3370 (SD 1030) mm^{-3} to 3170 (940) mm^{-3}; $P<0.01$) and lymphocytes increased (1870 (520) mm^{-3} to 2040 (580) mm^{-3}; $P<0.01$). We conclude that high concentrations of sevoflurane modified the distribution of leucocytes in anaesthetized patients. (*Br. J. Anaesth.* 1998; **80**: 502–503)

Keywords: anaesthetics volatile, sevoflurane; blood, leucocytes; blood, neutrophils; blood, lymphocytes

Previous studies have demonstrated that major surgical procedures combined with anaesthesia caused marked changes in leucocyte dynamics involving lymphopenia and neutrophilia.[1] However, few clinical reports have examined the effects of anaesthesia *per se* on leucocyte dynamics. We have recently shown *in vivo* that 2 MAC of sevoflurane anaesthesia induced leucocyte rolling and adhesion with microvascular endothelium in the rat mesentery via endothelial cell-dependent mechanisms.[2] If such events occur in a clinical situation, circulating leucocyte dynamics may be altered during anaesthesia. Therefore, we have examined if the number of circulating leucocyte subtypes was modified during sevoflurane anaesthesia.

Methods and results

After obtaining approval from our institutional Ethics Committee and informed consent, we studied 59 patients undergoing elective surgery under general anaesthesia. Exclusion criteria were: ASA II or more, patients more than 60 yr of age, those receiving preoperative transfusion or those with malignancy or inflammatory diseases. All patients received ranitidine 150 mg orally on the night before surgery, and hydroxyzine 50 mg and atropine 0.5 mg i.m. as premedication.

On arrival in the operating room, routine monitoring, including arterial pressure, ECG and pulse oximetry, was established. Arterial pressure was measured every 2 min throughout the study. Anaesthesia was induced with sevoflurane, which was increased by 0.5% every 4–5 breath up to 5%, in 100% oxygen (6 litre min^{-1}), using a semi-closed circle system. Ventilation was assisted at first and then changed gradually to being fully controlled for the next 20 min. Sevoflurane concentration at the Y-piece was confirmed by an anaesthesia gas analyser (Capnomac Ultima; Datex Instrumentation, Helsinki, Finland). During the study, acetated Ringer's solution 50–100 ml was given i.v. to obviate the dilutional effects on subsequent blood cell counting. Blood (2 ml) was obtained from the radial artery before and 20 min after induction of anaesthesia. Blood cells and leucocyte differential counting were performed using an automatic cell counter (SE-7000, Toa Medical Electronics, Tokyo).

Data are expressed as mean (SD), unless otherwise specified. The Student's *t* test was used to analyse the data where appropriate. $P<0.05$ was considered statistically significant.

Mean age of the study population was 31.8 (range 20–25) yr. Exhaled sevoflurane concentrations were within the range 4.3–4.7%. Sevoflurane significantly depressed systemic arterial pressure (from 121 (14) to 100 (14) mm Hg; mean −17.4%) ($P<0.05$). No patient required vasopressors to maintain arterial pressure. Similarly, heart rate increased from baseline values (78 (19) to 94 (14) beat min^{-1}; mean +20.5%) ($P<0.05$).

Changes in leucocyte numbers during sevoflurane anaesthesia are shown in figure 1. The total number of white blood cells remained constant during sevoflurane anaesthesia. While circulating lymphocytes increased significantly (mean +10.3%), the number of neutrophils decreased (−5.9%) from baseline values. Monocytes, eosinophils and basophils did not change significantly during the study.

Comment

Immune responses after anaesthesia and surgery are characterized by lymphopenia and granulocytosis, decreased lymphocyte transformation to various antigens and impaired neutrophil function, such as chemotaxis or oxygen radical production.[1] While surgical procedures are considered to play more important roles than anaesthesia *per se* on the postoperative alterations in immune function, previ-

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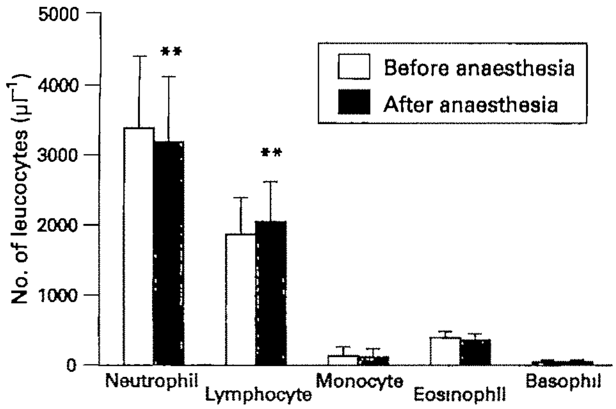

Figure 1 Changes in leucocyte numbers during sevoflurane anaesthesia. $^{**}P < 0.01$ compared with before anaesthesia.

ous *in vitro* studies demonstrated that leucocyte function was depressed significantly by exposure to anaesthetics in a dose-dependent manner.[3] However, few *in vivo* studies have examined the effects of anaesthesia *per se* on circulating leucocyte numbers. We have demonstrated that high concentrations of sevoflurane, even for a short time, decreased the number of circulating neutrophils and increased lymphocyte numbers. Interestingly, this finding is in agreement with a previous report that acupuncture analgesia caused a decrease in neutrophil counts and increased lymphocyte counts.[4]

There are several explanations for our results. Previous studies demonstrated that adrenal hormones such as corticosteroids were mainly responsible for redistribution of leucocytes between blood and other immune compartments.[5] Although we did not measure such hormones, the adrenosympathetic system during deep anaesthesia could have been depressed. Second, sevoflurane may modify leucocyte volume, resulting in miscounting of leucocyte subtypes by an automatic cell counter. However, even if leucocyte size was altered during sevoflurane anaesthesia, haemolysis before subtype measurements should have restored such changes. Furthermore, the internal density of leucocytes, which was another variable in subtype determination by the automatic counter, is unlikely to be affected by exogenous factors. Third, if neutrophil adhesion with endothelium occurred, as shown in animal studies,[2] the number of circulating neutrophils should have been depressed. Because of the observational data, however, these possibilities cannot elucidate the underlying mechanisms of the discrepancy between neutrophil and lymphocyte dynamics.

Another study showed that fluid loading with crystalloid caused an increase in circulating lymphocytes,[6] suggesting the possibility that lymphocytes are shifted into the intravascular space together with the bulk flow of fluid from the interstitium. As significant depression of systemic perfusion pressure during anaesthesia induces blood redistribution from non-vital to vital organs involving leucocyte dynamics, we did not examine other inhalation anaesthetics, such as halothane, at high concentrations in a clinical setting. Further studies are warranted to clarify the biological implications of such observations.

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British Journal of Anaesthesia 1998; **80**: 504–506

Thiopental or etomidate for rapid sequence induction with rocuronium?[†]

T. FUCHS-BUDER, H. J. SPARR AND T. ZIEGENFUß

Summary

We have assessed the effect of the choice of i.v. induction agent on intubation conditions, 60 s after administration of rocuronium 0.6 mg kg^{-1}. We studied 60 adult patients, allocated randomly to one of two groups. Anaesthesia was induced with alfentanil 10 µg kg^{-1} followed by thiopental 5 mg kg^{-1} (AT-R group; n=30) or etomidate 0.3 mg kg^{-1} (AE-R group; n=30). Both groups received rocuronium 0.6 mg kg^{-1}. Laryngoscopy was started 60 s later and intubation conditions were evaluated according to a standard score, which considered ease of laryngoscopy, condition of the vocal cords and reaction to intubation. In the AT-R group, overall intubation conditions were scored as excellent in 20 patients, good in nine and fair in the remaining patient. In the AE-R group, overall intubating conditions were excellent in 24 and good in six patients. The difference between the two groups was not significant. Of the three components of the intubation score assessed, response to intubation stimulus was significantly less pronounced in group AE-R compared with group AT-R (P<0.05): group AE-R, no reaction in 24 patients, slight diaphragmatic movement in five and mild coughing in one patient; group AT-R, no reaction in 13, slight diaphragmatic movement in 14, mild coughing in two and severe coughing in one patient. We conclude that etomidate as part of an induction regimen containing alfentanil and rocuronium attenuated the reaction to intubation to a greater extent than thiopental. (*Br. J. Anaesth.* 1998; **80**: 504–506)

Keywords: anaesthetic techniques, Induction; anaesthetics i.v., thiopental, anaesthetics i v., etomidate; neuromuscular block, rocuronium

Rocuronium has the fastest onset of action of the clinically available non-depolarizing neuromuscular blocking agents. Compared with the adductor pollicis muscle, the diaphragm is more resistant to the neuromuscular blocking properties of rocuronium, and onset of neuromuscular block is slower.[1] Thus neuromuscular block at the diaphragm may not be completely established when rocuronium is used for rapid sequence induction, leading to a diaphragmatic response to intubation in more than 50% of patients.[2] Using rocuronium ($2\times ED_{95}$) for rapid sequence induction, the choice of i.v. anaesthetic induction agent may be important in attenuating the reaction to intubation. It has been shown that opioids as part of the induction regimen improve rocuronium intubating conditions.[2] Gill and Scott reported that onset of vecuronium neuromuscular block was significantly shorter when anaesthesia was induced with etomidate (144±16 s) compared with thiopental (197±21 s) or propofol (206±21 s). They proposed etomidate as the i.v. induction agent of choice if rapid intubation of the trachea is required with a non-depolarizing neuromuscular blocking agent.[3] However, there is no information on whether etomidate rather than any other currently used i.v. induction agent improves the intubating conditions provided by other non-depolarizing neuromuscular blocking agents.

We hypothesized that induction of anaesthesia with etomidate may improve rocuronium intubating conditions at 60 s, by attenuating the diaphragmatic response to intubation. The aim of the study was to compare the effect of etomidate and thiopental on rocuronium ($2\times ED_{95}$) intubation conditions during rapid sequence induction.

Methods and results

After obtaining Ethics Committee approval and informed consent, we studied 60 ASA I–II patients, aged 18–70 yr, undergoing elective surgery under general anaesthesia. Patients with known neuromuscular disease or receiving medication known to influence neuromuscular function were excluded.

Patients were allocated randomly to one of two groups (n=30 in each), to receive thiopental (AT-R group) or etomidate (AE-R group) as the i.v. induction agent. Anaesthesia was induced with alfentanil 10 µg kg^{-1} followed by thiopental 5 mg kg^{-1} or etomidate 0.3 mg kg^{-1}, and rocuronium 0.6 mg kg^{-1} ($2\times ED_{95}$). All drugs were administered into a rapidly running i.v. infusion. Alfentanil, thiopental and etomidate were given over 10 s, followed by rocuronium, which was injected over 5 s. Sixty seconds after the end of injection of rocuronium, the trachea was intubated in all patients by the same experienced anaesthetist who was blinded to the drugs used. He assessed intubating conditions using the

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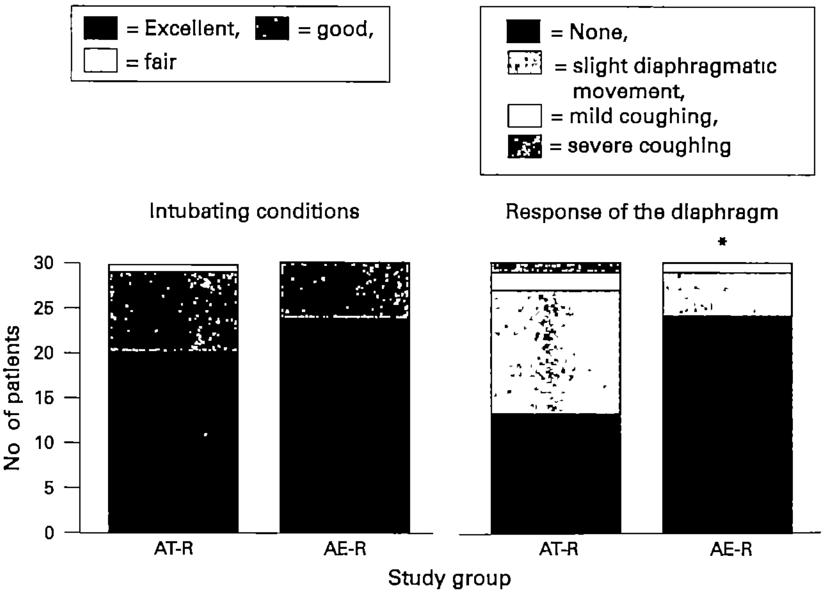

Figure 1 Overall intubation conditions (excellent, good or fair) and response of the diaphragm to tracheal intubation (none, slight diaphragmatic movement, mild coughing or severe coughing) after rapid sequence induction with alfentanil, thiopental and rocuronium (AT-R group) or alfentanil, etomidate and rocuronium (AE-R group). $^*P<0.05$ compared with group AT-R.

criteria of Cooper and colleagues[4] : ease of laryngoscopy (0=impossible, 1=difficult, 2=fair, 3=easy), condition of the vocal cords (0=closed, 1=closing, 2=moving, 3=open), response to tracheal intubation (0=severe coughing or bucking, 1=mild coughing, 2=slight diaphragmatic movement, 3=none). The three components are added together to give an overall intubation score for each patient. A score of 8–9 was considered excellent, 6–7 good, 3–5 fair and 0–2 poor. Cricoid pressure was applied during placement of the tracheal tube. Intubating time (time from start of intubation until definitive placement of the tube) was measured in both groups.

Analysis of overall intubation conditions between the two study groups was performed using Fisher's exact test. In both groups (AT-R and AE-R), there were insufficient numbers of patients who had fair or poor overall intubation conditions, and therefore for analysis, patients scoring excellent were compared with those not scoring excellent (good, fair or poor). The same procedure was performed for analysis of each of the three components of the intubation score. For an 80% chance of demonstrating a significant difference ($P<0.05$) between the AT-R and AE-R groups, a sample size of 28 was required.[5] The Mann–Whitney *U* test was used for statistical comparison; differences were considered significant when $P<0.05$. Patient characteristics and intubating time are expressed as mean (SD) or range.

The study groups did not differ in age or weight; group AT-R, mean age 45 (range 18–70) yr, mean weight 73 (SD 11.5) kg; group AE-R, age 45 (18–69) yr, weight 75 (15.8) kg. Intubating time was similar in both groups: group AT-R, 12.6 (3.0) s; group AE-R, 12.0 (2.5) s (ns). In group AT-R, overall intubating conditions were rated excellent in 20, good in nine and fair in one patient; in group AE-R, conditions were excellent in 24 and good in six patients (ns) (fig. 1). Of the three components of the intubation score, ease of laryngoscopy and condition of the vocal cords were similar in both groups (ease of laryngoscopy in group AT-R, easy in 26, fair in three and difficult in one patient, and in group AE-R, easy in 27 and fair in three patients (ns); condition of the vocal cords in group AT-R, open in 26 and moving in four patients, and in group AE-R, open in 28, moving in two patients (ns). However, the response to intubation was more pronounced in group AT-R (no reaction in 13, slight diaphragmatic movement in 14, mild coughing in two and severe coughing in one patient) compared with group AE-R (no reaction in 24, slight diaphragmatic movement in five and mild coughing in one patient) ($P<0.05$) (fig. 1).

Comment

We have investigated if induction of anaesthesia with etomidate, an anaesthetic with few side effects, may improve intubation conditions produced by rocuronium. The most important findings were that overall intubating conditions 60 s after administration of rocuronium ($2\times ED_{95}$) were good to excellent regardless of whether thiopental 5 mg kg^{-1} or etomidate 0.3 mg kg^{-1} was used as the i.v. induction agent. However, etomidate attenuated the reaction of the diaphragm to intubation to a greater extent than thiopental.

This may seem surprising as i.v. anaesthetics, in contrast with volatile anaesthetics, are generally thought not to interact with neuromuscular blocking drugs. However, they may influence intubation conditions in several ways: first, by depression of laryngeal and pharyngeal reactivity to the intubation stimulus. Propofol rather than thiopental may further facilitate intubation, as propofol depressed these reflexes to a greater extent than thiopental.[6] This may be relevant in situations in which the trachea is intubated without the use of neuromuscular blocking agents. However, when the induction regimen contains a neuromuscular blocker, intubating conditions after propofol did not differ from those after thiopental.[2] Second, the effects of some neuromuscular blocking agents may be potentiated directly by the i.v. anaesthetic. In this context, it has been shown that etomidate potentiates the neuromuscular blocking effect of pancuronium.[7] This has not been confirmed for rocuronium,[8] and the definitive role of this interaction remains speculative. Third, onset of neuromuscular block depends on both circulatory and non-circulatory factors. Circulatory factors determine the distribution of the neuromuscular blocking agents from the site of injection to the different muscles. Thus muscle perfusion, and consequently onset of neuromuscular block, may be affected by the i.v. anaesthetic. In this context, Gill and Scott reported a significant negative correlation between onset of neuromuscular block and change in mean arterial pressure; onset time was shortest when anaesthesia was induced with etomidate compared with thiopental or propofol.[3]

In this study, etomidate attenuated the reaction to intubation to a greater extent than thiopental; less diaphragmatic reaction occurred in group AE-R. If opioids (equivalent to alfentanil 20 $\mu g\ kg^{-1}$) and a higher dose of rocuronium ($3 \times ED_{95}$ rather than $2 \times ED_{95}$) are used, etomidate may improve intubating conditions further. This may be of interest if succinylcholine is contraindicated and rapid sequence induction is performed with rocuronium.

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Caudal anaesthesia with 0.375% ropivacaine or 0.375% bupivacaine in paediatric patients

M. J. Da Conceicao and L. Coelho

Summary

We have determined the effectiveness and degree of motor block produced by the new local anaesthetic, ropivacaine, when used for caudal anaesthesia in children. We studied 60 children, aged 3–6 yr, ASA I, allocated randomly in a double-blind manner, to receive one of two local anaesthetics: 0.375% ropivacaine 1.0 ml kg^{-1} or 0.375% bupivacaine 1.0 ml kg^{-1}. Patients were anaesthetized with continuous infusion of propofol 200 µg kg^{-1} min^{-1}. The lungs were ventilated with 50% nitrous oxide in oxygen. Heart rate and arterial pressure were measured every 5 min after administration of local anaesthetic until discharge from the recovery room. The extent of motor block in the recovery room was scored as 1–3. Adverse events and time to first analgesic requirements were recorded. Patients in the two groups did not differ in age, weight or height. There were no differences in heart rate or arterial pressure between the two groups. No adverse events were observed. The degree of motor block was significantly different between the two groups. The ropivacaine group showed a shorter duration of motor block than the bupivacaine group ($P<0.05$). Postoperative analgesia was required at a mean time of 5 (SD 3.2) h in the ropivacaine group compared with 5 (2.8) h in the bupivacaine group. These findings suggest that caudal anaesthesia with ropivacaine in paediatric patients is effective and produces less motor block in the postoperative period. (*Br. J. Anaesth.* 1998; **80**: 507–508)

Keywords: anaesthesia, paediatric; anaesthetic techniques, regional, caudal; analgesia, postoperative; anaesthetics local, ropivacaine; anaesthetics local, bupivacaine

Caudal block is a useful alternative to general anaesthesia or total i.v. anaesthesia as it provides effective postoperative analgesia. Unfortunately, motor block produced by caudal block may be a cause of distress to children in the postoperative period.[1]

Ropivacaine, a new long-acting local anaesthetic agent, offers a wider margin of safety than bupivacaine, with lower potential for central nervous system and cardiovascular side effects.[2] Ropivacaine also has greater sensory and fewer motor effects than bupivacaine.[3] In paediatric patients, this could allow more rapid mobilization after surgery. The aim of this study was to determine the effectiveness of the new local anaesthetic, ropivacaine, compared with bupivacaine for caudal anaesthesia in children.

Methods and results

After obtaining Institutional Ethics Committee approval and written informed consent from the parents of the patients, we studied 60 unpremedicated children, ASA I, aged 3–6 yr, undergoing elective lower abdominal surgery (orchidopexy) in a randomized, double-blind study. After an i.v. infusion of 0.9% saline was established, anaesthesia was induced with propofol 3 mg kg^{-1} containing 1% lidocaine 0.5 mg kg^{-1}, and alfentanil 30 µg kg^{-1}. No other opioid was used during operation. Tracheal intubation was facilitated with succinylcholine 2.0 mg kg^{-1}. No other neuromuscular blocking agents were used. Each patient was given a continuous infusion of propofol 200 µg kg^{-1} min^{-1}. The lungs were ventilated artificially with a mixture of 50% nitrous oxide in oxygen. After induction of anaesthesia, patients were turned to the left lateral position and a 22-gauge, short-bevelled needle was inserted into the sacral hiatus to produce caudal anaesthesia. The bupivacaine group (n=30) received 0.375% bupivacaine 1.0 ml kg^{-1} (maximum dose 3 mg kg^{-1}); the ropivacaine group (n=30) received 0.75% ropivacaine 1.0 ml kg^{-1}, diluted with 0.9% saline to 0.375% (maximum dose 3 mg kg^{-1}). Heart rate and arterial pressure were measured every 5 min after administration of local anaesthetic until discharge from the PACU. Motor weakness was determined according to a modified Bromage scale.[4] Postoperative pain was assessed by the Maunuksela score.[5] Adverse events were recorded. Analysis of variance was performed using the two-tailed Student's t test and chi-square test. $P<0.05$ was considered statistically significant. Results are presented as mean (SD, 95% confidence interval or range), as appropriate.

There were no differences between the groups in weight, height, age or duration of the surgical procedure. Mean heart rate, systolic and diastolic arterial pressures changed little in the two groups during the study. Severe hypotension or bradycardia was not observed in any patient. There was a significant difference in the degree of motor block between the

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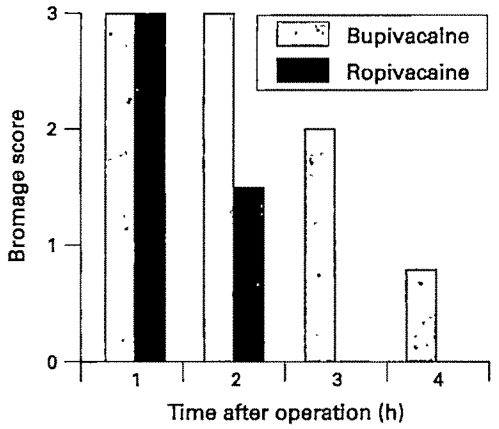

Figure 1 Motor block score on the Bromage scale in the postoperative period in the bupivacaine and ropivacaine groups. There was a significant difference between the two groups at 2, 3 and 4 h after operation but not after the first hour following operation.

two groups at 2, 3 and 4 h after completion of surgery (P=0.016) (fig. 1). There were no significant differences in Maunuksela pain scores in the PACU, or at 1, 2 or 3 h after operation, or on discharge from the PACU. There was no difference between the groups in time to first postoperative analgesia; mean 5 (SD 3.2) h after operation in the ropivacaine group and 5 (2.8) h in the bupivacaine group. No adverse events were observed.

Comment

We have confirmed that ropivacaine, administered to children by the caudal route, is an effective, long-acting local anaesthetic, producing less duration of motor block than bupivacaine. The modified Bromage scale,[4] a qualitative measure of the spread and intensity of muscle block, is easy to apply in a clinical setting. However, one criticism of the Bromage score is that it incorporates assessment of the degree of spread of local anaesthetic, in addition to the depth of motor block. A more sensitive assessment of motor function would be mechanical measurement of isometric muscle force in a single muscle group.[6]

Our results confirm previous reports in adults; less extensive and shorter duration of motor block was produced by ropivacaine compared with bupivacaine. The dose of ropivacaine could be adjusted to produce even less motor block with efficient sensory block. In our study, the concentration of local anaesthetic (0.375%) was higher than that used normally. This probably increased the intensity of the motor block. Perhaps future studies, using lower concentrations of ropivacaine (such as 0.2%), may demonstrate sensory block with even less motor block than that reported with 0.375% ropivacaine.

In summary, the results of this study confirm the suitability of ropivacaine for caudal anaesthesia in children. It appears to induce sensory block similar to that of bupivacaine, and motor block of shorter duration. This finding is useful in paediatric patients, especially as in addition, ropivacaine has minimal cardiovascular effects.

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Remifentanil in combination with propofol for spontaneous ventilation anaesthesia

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Summary

We have investigated the effect of four doses of remifentanil on the incidence of respiratory depression and somatic response at incision. Remifentanil was administered as a loading dose of 0.125, 0.25, 0.375 or 0.5 μg kg^{-1} and at a maintenance infusion rate of 0.025, 0.05, 0.075 or 0.1 μg kg^{-1} min^{-1}, respectively, with an infusion of propofol 6 mg kg^{-1} h^{-1}. Responses occurred in 88% of patients with remifentanil 0.025 μg kg^{-1} min^{-1} compared with 30–40% in the other groups. Respiratory depression after incision increased from 6% with remifentanil 0.025 μg kg^{-1} min^{-1} to 73% with 0.1 μg kg^{-1} min^{-1}. Increases in propofol infusion rate to 7.2–8.4 mg kg^{-1} h^{-1} produced adequate maintenance of anaesthesia. Reductions in remifentanil doses to 0.025–0.05 μg kg^{-1} min^{-1} resulted in adequate respiration at the end of surgery in 88% of patients. Maintenance infusions of the two drugs for spontaneous ventilation are likely to be in these ranges. However, the ideal loading doses and infusion rates for induction remain to be established. (*Br. J. Anaesth.* 1998; **80**: 509–511)

Keywords: anaesthetics i.v., propofol; analgesics opioid, remifentanil; ventilation, spontaneous

An anaesthetic regimen for spontaneous ventilation requires a technique that does not cause prolonged respiratory depression. Opioids such as fentanyl and alfentanil are often included as part of a balanced anaesthetic as they reduce the amount of concomitant agent required for the procedure[1] but have the disadvantage of clinical effects extending into the postoperative period. Short-acting drugs allow better titration of anaesthesia and may therefore reduce the incidence of respiratory depression and permit rapid recovery, which is especially desirable for day-case surgery.[2] Remifentanil is a rapidly acting ester opioid, which is metabolized by non-specific esterases. This results in a much higher clearance and shorter elimination half-life (<10 min) than other opioids, and allows administration by infusion without accumulation.[3] Remifentanil has been administered to volunteers breathing spontaneously and to patients undergoing controlled ventilation.[4] However, dose responses during total i.v. anaesthesia (TIVA) with propofol and spontaneous ventilation are not known.

Methods and results

This was an open, randomized, two-centre study. After obtaining approval from the local Ethics Committee and written informed consent, we studied 64 ASA I or II patients, aged 18–65 yr, undergoing elective surgery lasting more than 30 min and involving skin incision. Exclusion criteria were patients receiving opioids, clonidine or benzodiazepines, those sensitive to any of the proposed anaesthetic drugs and pregnancy.

Patients were allocated randomly to receive one of four remifentanil regimens consisting of a loading dose administered over 1 min and a maintenance infusion commencing simultaneously with the loading dose. After arrival in the anaesthetic room, separate cannulae were inserted for administration of remifentanil and propofol, and standard anaesthetic monitoring commenced with values recorded every 5 min increasing to every minute in the presence of respiratory depression. After 3 min of preoxygenation, the remifentanil loading dose and infusion were commenced at 0.125 μg kg^{-1} and 0.025 μg kg^{-1} min^{-1}, 0.25 μg kg^{-1} and 0.05 μg kg^{-1} min^{-1}, 0.375 μg kg^{-1} and 0.075 μg kg^{-1} min^{-1} or 0.5 μg kg^{-1} and 0.1 μg kg^{-1} min^{-1}.

Three minutes after administration of the remifentanil loading dose, anaesthesia was induced by infusion of propofol 50 mg min^{-1} until loss of consciousness. A laryngeal mask airway was placed and ventilation with a minimum of 33% oxygen in air commenced. Anaesthesia was maintained using an infusion of propofol 6 mg kg^{-1} h^{-1}, with the remifentanil infusion rates as described above until skin incision, when patients were observed for somatic response or respiratory depression. Somatic response was defined as somatic movement, an increase in systolic arterial pressure by 15 mm Hg above baseline or heart rate >90 beat min^{-1}. Respiratory depression was defined as a mean end-tidal carbon dioxide partial pressure greater than 7.2 kPa or ventilatory frequency less than 8 bpm, or both.

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Table 1 Patient characteristics, incidence of respiratory depression and inadequate anaesthesia, and final drug infusion rates for the four remifentanil groups

	Remifentanil infusion rate (μg kg^{-1} min^{-1})			
	Group 1 0.025	Group 2 0.05	Group 3 0.075	Group 4 0.1
n	16	17	16	15
Sex (M/F)	11/5	14/3	6/10	7/8
Age (yr) (mean (range))	40 (21–64)	39 (19–65)	41 (19–59)	42 (24–58)
Weight (kg) (mean (range))	76.9 (51–115)	75.0 (55–105)	73.7 (56–94)	70.6 (51–95)
ASA (I, II)	13,3	14,3	14,2	13,2
Duration of anaesthesia (min) (median (range))	41 (21–99)	43(17–138)	61(19–98)	59 (28–82)
Respiratory depression at skin incision (*n* (%))	1 (6%)	7 (41%)	11 (69%)	11 (73%)
Response to incision (*n* (%))	14 (88%)	5 (29%)	6 (38%)	5 (33%)
Final remifentanil infusion rate (μg kg^{-1} min^{-1}) (mean (range))	0.03 (0.01–0.05)	0.04 (0.01–0.07)	0.04 (0.01–0.07)	0.05 (0.01–0.1)
Final propofol infusion rate (mg kg^{-1} h^{-1}) (mean (range))	8.4 (6.2–11.9)	7.7 (6.0–14.0)	7.6 (6.0–15.1)	7.2 (5.9–11.8)
Adequate respiration at end of surgery (*n* (%))	16 (100%)	13 (77%)	14 (88%)	13 (87%)

Manual ventilation was provided to maintain oxygen saturation >94% until resolution of respiratory depression. After incision, the infusion rates of the two drugs were titrated according to response. In the presence of respiratory depression, remifentanil was reduced in pre-defined steps of 0.025 μg kg^{-1} min^{-1} or by 50% if the infusion rate was already 0.025 μg kg^{-1}min^{-1} or less. The propofol infusion rate was titrated upwards with 20-mg increments and steps of 1 mg kg^{-1} h^{-1} if somatic movement occurred in response to surgical incision. Both remifentanil and propofol infusions were continued until after the last suture was inserted, at which time postoperative analgesia, consisting of local anaesthesia or non-steroidal anti-inflammatory agents, or both, was administered, as indicated clinically.

Patient characteristics and surgery (primarily hernia repair and varicose vein surgery) were similar in all groups although there were more males in groups 1 and 2 (table 1). At skin incision somatic responses occurred in 88% of patients at an infusion rate of remifentanil of 0.025 μg kg^{-1} min^{-1} compared with 30–40% in the other groups. The majority of patients required additional propofol to maintain anaesthesia and the final mean propofol infusion rate was 7.2–8.4 mg kg^{-1} h^{-1}. Respiratory depression after incision increased with higher doses of remifentanil and occurred in 73% of patients receiving remifentanil infusions of 0.1 μg kg^{-1}min^{-1}. By the end of surgery, 76–100% of all patients had adequate respiration after reductions in remifentanil infusion rates to 0.026–0.053 μg kg^{-1} min^{-1} (table 1).

Postoperative questioning revealed no evidence of intraoperative awareness in any patient. The overall incidence of postoperative nausea and vomiting was 7% and 1%, respectively, which was not dose dependent.

Comment

There was a high incidence of respiratory depression immediately after surgical incision which was compounded by administration of a loading dose of remifentanil and was least at the lowest dose of 0.125 μg kg^{-1}. Remifentanil was given in this manner in order to achieve steady state plasma drug concentrations more rapidly. However, mean maintenance infusions of remifentanil of 0.026–0.053 μg kg^{-1} min^{-1} permitted adequate respiration in 88% of patients at the end of operation and only one patient was still apnoeic at the end of surgery.

The high incidence of somatic responses seen at incision (29–88%) were caused, at least in part, by the low initial infusion rate of propofol (6 mg kg^{-1} h^{-1}) which was selected to identify the remifentanil dose response. The same pattern of response was seen by Hogue and colleagues[4] in patients undergoing ventilation; they used a propofol infusion rate of 4.5 mg kg^{-1} h^{-1} with higher remifentanil infusion rates of 0.5 and 1.0 μg kg^{-1} min^{-1}, which were reduced by 50% after tracheal intubation. They found that 19% and 23% of patients required propofol rescue medication for light anaesthesia, confirming that adequate hypnosis is required in addition to potent doses of opioids to ensure that somatic responses are prevented during anaesthesia. The final propofol infusion rates of 7.2–8.4 mg kg^{-1} h^{-1} were higher at the lower remifentanil infusion rates but were lower than the ED$_{95}$ of 21 mg kg^{-1} h^{-1} for propofol and nitrous oxide anaesthesia in patients premedicated with lorazepam.[5]

Remifentanil can be administered as part of a TIVA technique with propofol for spontaneous ventilation anaesthesia. An infusion of 0.05 μg kg^{-1} min^{-1} or less was associated with adequate ventilation in the majority of patients, and in combination with a propofol infusion of 7.2–8.4 mg kg^{-1} h^{-1} provided clinically acceptable maintenance of anaesthesia. Induction of anaesthesia after a loading dose of remifentanil greater than 0.125 μg kg^{-1} min^{-1} (group 1) was associated with a high incidence of respiratory depression, while inadequate anaesthesia was found for surgical incision with an infusion of propofol 6 mg kg^{-1} h^{-1}. Further studies are necessary to identify the appropriate combination of loading dose and initial infusion rates of the two drugs and to elucidate the efficacy of such a combination for clinical anaesthesia.

Acknowledgement

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British Journal of Anaesthesia 1998; **80**: 512–515

CASE REPORTS

Extradural anaesthesia for Caesarean section in a patient with syringomyelia and Chiari type I anomaly

M. R. Nel, V. Robson and P. N. Robinson

Summary

We describe elective Caesarean section performed under extradural anaesthesia in a parturient with symptomatic syringomyelia and co-existing Chiari type I anomaly. Syringomyelia is reviewed and the anaesthetic implications of the condition discussed. Anaesthesia should be directed primarily at avoidance of increased intracranial pressure, which can cause sudden deterioration in these patients. (*Br. J. Anaesth.* 1998; **80**: 512–515)

Keywords: complications, syringomyelia; complications, Chiari anomaly; anaesthesia, obstetric; anaesthetic techniques, extradural

Syringomyelia is an unusual neurological condition characterized by cystic degeneration within the spinal cord. The Chiari type I anomaly (also termed Arnold–Chiari type I anomaly) is one of a group of congenital abnormalities associated with descent of the hindbrain structures through the foramen magnum. We report the successful use of extradural anaesthesia for elective Caesarean section in a woman with both of these conditions.

Case report

A 31-yr-old woman, para 1, known to have syringomyelia and a related Chiari type I anomaly, was admitted for elective Caesarean section at 38 weeks' gestation. Her neurological condition had been diagnosed after an MRI scan (fig. 1), performed 3 months before she became pregnant. Her previous obstetric history included spontaneous vaginal delivery of a healthy infant at term, using only i.m. pethidine as analgesia.

The MRI scan was performed to investigate a history of continuous pain in the right side of the neck, radiating to the right shoulder, which had begun approximately 2 yr earlier. The patient also had recurrent occipital headaches, aggravated by coughing or sneezing. Careful neurological examination after the scan had revealed reduced sensation to pain and temperature from C2 to approximately T8 on the left side, correlating with the appearance on the scan of the extent of the syrinx. She also had depressed reflexes in the left arm and wasting of the left thenar eminence.

After the MRI scan, the patient was assessed by a neurosurgeon who recommended urgent foramen magnum decompression to relieve her neck pain and headaches, and prevent her neurological deficit from worsening. However, she declined surgical intervention and subsequently became pregnant. During the second and third trimesters her headaches intensified, but she continued to refuse surgery. After advice from the patient's neurologist and neurosurgeon, it was decided that an elective Caesarean section would be the method of delivery least likely to aggravate the syrinx.

At the preoperative visit the patient's body weight was 58 kg and height 155 cm. Neck mobility and mouth opening were assessed as normal. Her lumbar spine had a mild scoliosis, concave to the right, but the spinous processes were easily palpable. Premedication comprised ranitidine 150 mg orally the night

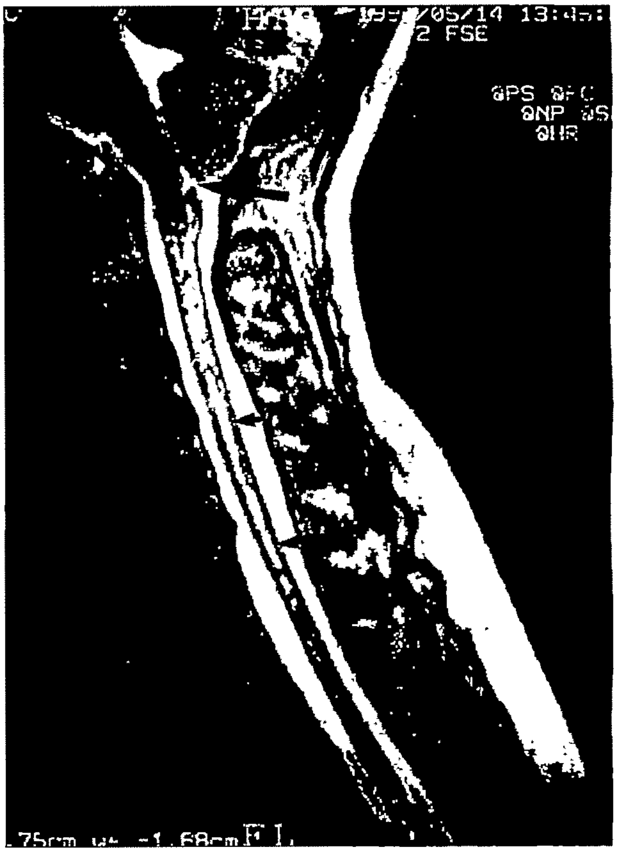

Figure 1 T2-weighted sagittal MRI of the upper spinal cord and brainstem The syrinx (small arrows) appears discontinuous because of the thin slice. The Chiari type I anomaly is also indicated (large arrow).

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before surgery, repeated on the morning of surgery together with metoclopramide 10 mg.

On arrival in the operating theatre a 16-gauge peripheral i.v. cannula was inserted, and the patient was given Hartmann's solution 1000 ml as a preload. Monitoring consisted of pulse oximetry, ECG and non-invasive automated arterial pressure. The sitting position was chosen because of patient preference. Using a 16-gauge Tuohy needle, the extradural space was located by loss of resistance to air and catheterized at the L2–3 interspace. The patient was then placed supine with left lateral tilt. Extradural anaesthesia was established by slowly injecting 3–4-ml bolus doses at 5-min intervals, using a total of 20 ml of 0.5% bupivacaine, to which had been added fentanyl 50 μg. Supplementary oxygen was given by face mask and 35 min after the first bolus the height of the block was assessed as T4 bilaterally. Surgery was started and a healthy baby weighing 2680 g was delivered 12 min later; this was followed by slow i.v. injection of oxytocin 10 u. Caesarean section proceeded uneventfully, and Hartmann's solution 1000 ml was given i.v.; blood loss was estimated at 350 ml. The patient remained haemodynamically stable and no vasopressors were required.

Postoperative analgesia consisted of morphine 7.5–10 mg i.m. every 3 h as required, rectal diclofenac up to 150 mg per 24 h and oral co-dydramol. Her neurological condition remained unchanged. She recovered well from the Caesarean section and was discharged on day 4 after operation.

Seven weeks after delivery the patient was reviewed: she continued to have neck pain and headaches but there had been no neurological deterioration. She remains reluctant to undergo neurosurgery, but is currently awaiting elective admission for sterilization.

Discussion

Syringomyelia is characterized by the presence of an expanding, longitudinal cystic cavity (syrinx) within the spinal cord. Ollivier d'Angers (1827) coined the term syringomyelia[1] from two Greek roots meaning "channel" and "marrow". It is an uncommon condition, with a prevalence of 8.4 per 100 000 identified in an urban English setting.[2]

The pathogenesis of syringomyelia has been the subject of controversy; however, the distinction proposed by Williams (1969) between "communicating" and "non-communicating" forms[3] is now accepted widely. The communicating form is the more common; this implies an initial or persisting continuity between the syrinx and CSF in the central canal of the cord. In the non-communicating form there is usually an association with spinal trauma, arachnoiditis or a spinal tumour.

Most cases of communicating syringomyelia are linked with congenital or acquired anomalies involving the foramen magnum, of which the Chiari type I anomaly (herniation of the cerebellar tonsils below the foramen magnum) is the commonest.[4] There is a strong association, and probably a causal relationship, between traumatic birth and subsequent development of the cerebellar ectopia and communicating syringomyelia.[5]

The foramen magnum abnormalities cause intermittent obstruction to CSF outflow from the fourth ventricle, with the development of craniospinal pressure dissociation,[5] a relatively higher CSF pressure in the head and lower pressure in the spine. This pressure dissociation may not be apparent if only baseline intraventricular and lumbar CSF pressures are studied, but is usually measurable after an episode of increased thoracoabdominal pressure, for example after a cough or Valsalva manoeuvre. The resultant increase in CSF pressure is more pronounced and more sustained in the intraventricular CSF.[5] Development of a craniospinal pressure gradient is believed to be associated with intermittent propagation of pressure waves into the central canal, which eventually causes dissection into adjacent neural tissue.[4] The resultant syrinx typically arises in the lower cervical or upper thoracic region; expansion is characteristically very gradual, initially into the anterior and lateral cord. Extension upwards into the medulla often occurs (syringobulbia), whereas involvement of the lumbar cord is uncommon.

In the non-communicating form the syrinx may develop anywhere in the cord. Factors involved in initiating cavitation may include haematoma formation, ischaemia, venous obstruction, shearing stress with mechanical disruption and secretion of proteinaceous fluid.[1 4 5] Subsequent progression of the syrinx may depend on a CSF pressure gradient developing across the lesion, as in the communicating form.[5]

The clinical picture is consistent with atrophy of anatomically susceptible spinal cord and brainstem tissue. A classic case of communicating syringomyelia presents with asymmetrical loss of pain and temperature sensation in the upper limbs (lateral spinothalamic tracts), lower motor neurone signs ascending from the hands (anterior horn cells) and upper motor neurone signs in the lower limbs (corticospinal tracts). The presence of posterior column signs usually signifies advanced disease.[4] Involvement of the autonomic nervous system is not uncommon. Trophic changes may be striking, particularly the development of gross osteoarthropathy (Charcot's joints). Syringobulbia is most commonly denoted by trigeminal or vagus nerve dysfunction; other cranial nerves which may be affected include the third, sixth, seventh, ninth and 12th.[4 6] Symptoms may arise independently from a coexisting Chiari type I anomaly; these are often related to Valsalva-type manoeuvres, and include paroxysmal headaches, neck pain, syncope, vertigo, weakness and sensory disturbance.[5 7 8]

Currently, the commonest operation performed for communicating syringomyelia involves decompression at the foramen magnum.[9 10] Best results are obtained when surgery is performed relatively early in the course of the disease. Without surgical intervention, the natural history follows one of three patterns: chronic progressive disease, chronic stable disease or, occasionally, rapid onset of severe disability within a few years of diagnosis.[6]

Mean age at onset of symptoms is 25–40 yr.[2 4 6] However, cases of syringomyelia are now detected frequently in childhood as a result of increasing use of MRI, particularly in evaluating scoliosis.[11] Therefore, it is expected that a number of female patients with known syringomyelia will require obstetric anaesthesia, although there appears to be only one previous case report in the literature.[12]

Before an anaesthetic plan can be formulated, a thorough neurological appraisal is necessary, including MRI scan. Several associated abnormalities may have specific implications for anaesthesia–kyphoscoliosis, pes cavus, cervical ribs, fusion of cervical vertebrae (Klippel–Feil syndrome), hydrocephalus and spina bifida,[4–6] in addition to the presence of a Chiari type I anomaly or other foramen magnum disorder.[7]

Neurological assessment must incorporate a check for evidence of autonomic neuropathy; cardiac autonomic neuropathy is more likely when there is coexisting syringobulbia.[13] The diagnosis is best made by performing a series of simple bedside tests,[12–14] although the presence of a prolonged corrected QT interval (QT$_c$) has proved a useful single indicator in diabetic patients.[14] Prior identification of autonomic involvement is important as these patients commonly exhibit tachyarrhythmias and a widely fluctuating arterial pressure in response to the stress of anaesthesia and surgery. Moreover, sudden cardiac or respiratory arrest has been attributed to autonomic neuropathy in syringomyelia patients after posterior fossa surgery,[13] and in diabetic patients after general or regional anaesthesia.[14,15] Further considerations include possible delayed gastric emptying, urinary bladder dysfunction and impaired thermoregulation.

If syringomyelia involves the respiratory muscles or there is significant associated kyphoscoliosis, pulmonary function tests should be performed. These tests can also indicate the presence of unsuspected vocal cord abductor paresis by a characteristic flattening of the inspiratory curve on a flow–volume loop.[8]

Where trophic changes in the skin are widespread, peripheral venous access may be limited. Acrocyanosis of the hands may be a feature,[4] with the potential for confusion over central oxygenation status. There may be disorganized joints, demineralization of bone and fixed flexion deformities,[4] requiring careful movement and positioning of these patients to avoid pathological fractures and soft tissue ischaemia. Areas of sensory loss increase the potential for inadvertent injury to occur, even in the conscious patient.

In our opinion one of the most important goals of anaesthesia is to avoid aggravating the already disturbed craniospinal pressure relationship. Even in patients without symptoms of increased intracranial pressure, and without clinical or radiological hydrocephalus, it can be assumed that intracranial CSF pressure is *relatively* high as this is fundamental to the pathophysiology of communicating syringomyelia. Sudden clinical deterioration in syringomyelia after coughing or straining is well recognized.[4,9] It follows that an appropriate anaesthetic technique has to avoid any further increase in intracranial pressure. This is particularly applicable to the use of general anaesthesia: there are reports of deterioration after general anaesthesia for non-cranial surgery, when no specific attempt was made to control intracranial pressure.[8,12]

General anaesthesia requires careful prior airway assessment and planning. Intubation may be complicated further by the need to avoid succinylcholine if significant muscle denervation has occurred, because of the risk of a hyperkalaemic response.[16] In addition, increased sensitivity to non-depolarizing neuromuscular blocking agents has been demonstrated in syringomyelia.[17]

An earlier case report ruled out regional anaesthesia for medico–legal reasons.[12] However, the presence of active neurological disease is no longer considered an absolute contraindication to regional anaesthesia.[18] We believe an extradural anaesthetic offers several advantages over general anaesthesia in these patients: the potential hazards of securing the airway are avoided, respiratory function is less compromised and the existing craniospinal CSF pressure relationship is better preserved. Extradural block should be established very slowly: first, to avoid the precipitate decrease in arterial pressure that may occur if there is autonomic neuropathy and second, to avoid sudden distension of the extradural space. Such distension may induce significant subarachnoid compression, thereby both increasing intracranial pressure[19] and creating a potentially damaging pressure wave within the syrinx.[5]

We suggest that spinal anaesthesia is best avoided in syringomyelia, particularly in the presence of a co-existing Chiari malformation, as there are case reports describing the onset of signs and symptoms up to 2 weeks after dural puncture.[20,21] Whatever the mode of anaesthesia, these patients require close postoperative observation, particularly if there is syringobulbia, autonomic neuropathy or recently progressive disease, when sudden apnoea or cardiac arrest may be more likely.

The decision to perform a Caesarean section in this case was an interdisciplinary one, with the full agreement of the woman concerned. In the absence of existing guidance in the literature, others may have opted to permit labour. In this event, we would recommend early siting of an extradural catheter and strict avoidance of straining during the second stage.

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Anaesthetic management in patients suspected of, or at risk of, having Creutzfeldt–Jakob disease

J. Hernández-Palazón, J. F. Martínez-Lage, J. A. Tortosa and J. M. García-Cayuela

Summary

We report two young patients who had repeated neurosurgical procedures and who were thought to be at risk of developing Creutzfeldt–Jakob disease (CJD). The first patient had been given a lyophilized dural graft in the course of removal of a cerebellar medulloblastoma 15 yr previously. The second patient had received pituitary-derived growth hormone for treatment of growth hormone deficiency, secondary to a third ventricle teratoma, excised 13 yr earlier. The presence of cerebellar symptoms together with being recipients of growth hormone or dural graft of cadaveric extraction arose suspicion of a diagnosis of CJD in both individuals. Precautions in the anaesthetic and surgical management of these two patients are discussed, and pertinent literature is reviewed briefly. (*Br. J. Anaesth.* 1998; **80**: 516–518)

Keywords: complications, Creutzfeldt–Jakob disease; hormones, growth

Creutzfeldt–Jakob disease (CJD) is a lethal form of dementia that progresses to produce myoclonus and cerebellar symptoms. It has a worldwide reported annual incidence of 1 per million.[1] This disease, and other spongiform encephalopathies, are thought to be caused by replication of an unconventional transmissible agent, the prion.[2] The pathogenesis of the spontaneous form of CJD is still unknown. On the contrary, CJD has been transmitted experimentally to diverse animal species, and accidentally to humans by means of contaminated instruments and grafts, or by hormones of cadaveric origin.[3] We recently reported four patients who were diagnosed as having CJD after implants of lyophilized dura mater grafts obtained from cadavers.[4] This experience, in addition to increasing awareness of the possibility of accidental iatrogenic transmission of CJD, especially in recipients of cadaveric dural grafts and hormones,[1 3–5] prompted us to report the precautions used during anaesthesia for neurosurgery in two patients in whom CJD was a possible diagnosis.

Case reports

PATIENT NO. 1

A 17-yr-old boy presented in 1982 with a 3-month history of headaches, vomiting and cerebellar symptoms. After a diagnostic work-up the patient underwent a posterior fossa craniectomy with complete excision of a large cerebellar tumour (a medulloblastoma). Dural closure was achieved with the aid of a lyophilized commercial dura mater graft (Lyodura). He was also treated with a ventriculoperitoneal (VP) shunt, cobalt therapy for the whole head and spinal axis (total dose of 52 Gy), and chemotherapy (vincristine and CCNU). In 1986, the patient presented with local tumour recurrence in the right cerebellar hemisphere, which was treated with a second course of local radiotherapy and further chemotherapy.

In 1997, at the age of 32 yr, the patient was found on a routine follow-up evaluation to have dizziness, mild unsteadiness and dysmetria of his right hand. Post-irradiation necrosis, tumour recurrence, VP shunt failure and CJD were considered in the differential diagnosis. The EEG showed non-specific bursts of irregular bioelectrical activity. Computerized tomography (CT) scan and magnetic resonance imaging (MRI) disclosed a 3.5-cm right cerebellar lesion that was enhanced after i.v. contrast administration. A single photon emission computed tomography (SPECT) study suggested that the lesion was a tumour recurrence. On February 25, 1997, the patient underwent a second posterior fossa procedure. The personnel entering the operating room wore waterproof surgical caps and gowns, two pairs of gloves, and face masks with plastic transparent shield visors. I.v. cannulation was achieved with a peripheral venous cannula. Anaesthesia was induced with thiopental 5 mg kg^{-1} and fentanyl 5 μg kg^{-1}, tracheal intubation was facilitated by vecuronium 0.15 mg kg^{-1}, and anaesthesia was maintained with isoflurane 1–1.2 MAC and oxygen in air ($F_{I_{O_2}}$ 0.4), fentanyl 2 μg kg^{-1} h^{-1} and vecuronium 0.1 mg kg^{-1} h^{-1}.

During the surgical procedure the tumour was removed and several tissue samples obtained from the adjacent cerebellum and dura mater were sent for histopathological study, which confirmed recurrence of the medulloblastoma and excluded the diagnoses of CJD and radio-necrosis. The disposable anaesthetic equipment was incinerated, and the laryngoscope was washed thoroughly and immersed in a 5% solution of sodium hypochlorite for 1 h. The walls and floor of the operating theatre, operating table and anaesthetic

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equipment were cleaned with a 0.5% solution of sodium hypochlorite. Most of the surgical tools were disposable and were discarded and incinerated, and the remainder were disinfected with a sodium hypochlorite solution, followed by two cycles of autoclaving at 134°C for 18 min. As of October 1997, the patient was asymptomatic and a repeat post-contrast CT scan showed complete tumour removal.

PATIENT NO. 2

A 14-yr-old boy was admitted to hospital for the first time in 1982 with symptoms and signs of increased intracranial pressure and panhypopituitarism. After a diagnostic evaluation, which included angiography and air ventriculography, the boy underwent removal of a giant immature teratoma of the third ventricle via a transcallosal approach and received radiotherapy (total dose 60 Gy). He subsequently developed isolated dilatation of the left lateral ventricle that was treated with an unsuccessful neuroendoscopic procedure for the opening of an obliterated foramen of Monro, followed by placement of a ventriculoperitoneal (VP) shunt. Because of panhypopituitarism, he was being seen by an endocrinologist and received replacement therapy, which included administration of extracted growth hormone from 1975 to 1983.

In January 1996, he was diagnosed as having cerebrospinal fluid over-drainage and the VP shunt was changed to a high-pressure system. After this procedure the patient developed dizziness, dysarthria, blurred vision and ataxia. At this time the following differential diagnoses were considered: tumour dissemination, radio-necrosis, cranioencephalic disproportion, shunt malfunction and CJD. A CT scan showed overcrowding of the posterior fossa structures without significant signs of tumour dissemination and the cranial bones were considerably thickened indicating long-standing intracranial decompression. MRI revealed descent of the cerebellar tonsils. An electroencephalogram (EEG) showed diffuse generalized slow waves. On February 27, 1996, the patient underwent posterior fossa decompression for acquired tonsillar herniation using the same precautions as those described for patient No. 1. A biopsy of cerebellar tissue ruled out the presence of CJD. Subsequently, the patient deteriorated and died on December 29, 1996. Permission for autopsy was denied.

Discussion

CJD is a degenerative disease of the central nervous system, which progresses to produce dementia and myoclonus.[1] CJD is one of the transmissible subacute spongiform encephalopathies.[1] Other diseases belonging to the same group are kuru, fatal familial insomnia, Gerstmann–Straussler–Scheinker syndrome and probably Alpers disease in humans, and bovine spongiform encephalopathy ("mad cow disease") and scrapie in animals. The histopathological background is spongy degeneration of the grey matter.[1] CJD has a very low incidence in the general population (1–2 cases per million inhabitants yearly).[1] It has a very long incubation period (many months or even years). CJD usually leads to death within 1 yr. At present, there are no diagnostic tests and there are no vaccines or treatment. Presentation of CJD in humans can happen sporadically (90% of cases), it may also be familial (8%) or a result of iatrogenic causes (2–3%).

CJD is caused by an unconventional agent, the prion,[2] which is resistant to all methods of sterilization. The disease develops by accumulation in the central nervous system (CNS) of an abnormal prion protein (PrP) normally present in the brain and is thought to act as a neurotransmitter. The production of PrP is encoded by a gene located on the short arm of chromosome 20. The familial forms of CJD are associated with several mutations in codon 129 of this gene. Sporadic and iatrogenic forms of CJD are associated with homozygosity at codon 129 of the PrP gene. Sporadic CJD normally presents in patients older than 50 yr.

Iatrogenic CJD[3] has been described in humans in three circumstances: (1) after the use of insufficiently sterilized surgical equipment[1 3]; (2) after use of extracted pituitary hormones (mainly growth hormone)[6]; and (3) after implant of contaminated grafts of human extraction (corneal and dural grafts).[3–8] Iatrogenic CJD should be suspected in young patients with rapidly evolving ataxia and visual problems, which are followed by late deterioration in mental status and myoclonus. Differential diagnosis is difficult because growth hormone and dural graft recipients have already had previous neurological diseases, such as cerebral and cerebellar tumours, congenital malformations of the CNS, or may have been treated with radiotherapy or VP shunts, increasing the possibilities of tumour recurrence, radio-necrosis or VP shunt malfunction.

The main risk of transmission of CJD is during cerebral biopsy for diagnostic confirmation of the disease. But there are other patients that may be incubating CJD. Individuals at risk are those treated with extracted pituitary hormones before 1985, when recombinant growth hormone was commercialized,[3 6] and recipients of dural grafts of cadaveric origin,[3 4 7 8] especially those who were given Lyodura and those grafted before 1987, when manufacturers changed the procedures of procurement and sterilization of these implants. Having seen four iatrogenic cases of CJD after Lyodura implants in our hospital,[4] we were particularly interested in this problem and have reviewed the currently accepted measures for stopping CJD transmission among neurosurgical patients, and for preventing contamination of anaesthetists and other operating room personnel. During 1983 and 1984, 1052 neurosurgical operations were undertaken at our hospital. We identified 37 patients who had been given a dural graft. Nineteen of these individuals had already died of their original diseases or unrelated causes. Four individuals developed CJD,[4] and the survivors are being submitted to yearly reviews. A study of codon 129 of the PrP gene in these 17 survivors showed that seven were homozygous for methionine, four for valine, and six were heterozygous. Accordingly, 11 of 17 (65%) of the recipients of dural grafts were homozygous at codon 129, a condition that seems to predispose to contracting exogenous prion infection,[5] and they are considered among the individuals at risk of developing CJD. Several publications have emphasized that health care workers are over-represented in relation to lay people with regard to the incidence of CJD.[9]

Patients known to have, or suspected of having, CJD should be managed in the hospital ward with precautionary measures similar to those used in patients with hepatitis B or acquired immune deficiency syndrome (AIDS). When possible, disposable items should be used and incinerated afterwards. For sampling and processing of biological specimens, personnel should use gloves, masks and eye protection. Catheters and needles, including those used for lumbar puncture, EEG and EMG recording, should be destroyed. Pins used for routine testing of pain sensation during neurological examinations must be discarded after use in any patient. Potentially contaminated biological products, including secretions, blood, CSF and other body fluids, must be incinerated.

In anaesthesia,[10 11] it is recommended to destroy all disposable equipment and to sterilize the laryngoscope by immersion in a 5% sodium hypochlorite solution for 1 h. Disposable equipment is mandatory for patients at risk of developing CJD who require neurosurgery or eye operations, and even disposal of surgical instruments is highly recommended.[11 12] Surgery in these patients should be performed at the end of the operating list to allow for thorough cleaning and disinfection of equipment and operating room. Personnel attending the operation should be kept to a minimum and should wear waterproof gowns, gloves and face masks with transparent plastic visors to protect the eyes. The equipment used in patients at risk of CJD undergoing operations other than neurosurgery or ocular surgery should be cleaned by trained personnel and subjected to chemical disinfection with sodium hypochlorite for 1 h in the case of aluminium or zinc instruments, and sodium hydroxide 1 or 2 N for 1 h for stainless steel tools. After this, the equipment should be autoclaved at 134°C (30 kg cm^{-2}) for 1 h, or subjected to two cycles of autoclaving at 134°C of 18 min each.

In our view, common sense, knowledge of the methods of CJD transmission in the hospital milieu, and use of precautionary measures for potential risks may minimize the danger of CJD propagation among care workers and other patients.[13]

Acknowledgement

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Minimally invasive coronary bypass surgery: postoperative pain management using intermittent bupivacaine infiltration

M. F. BORGES AND A. S. COULSON

Summary

Minimally invasive direct coronary artery bypass grafting (MIDCAB) is becoming a popular adjunct to standard cardiac bypass surgery in selected patients with accessible single or double vessel disease. However, the limited anterior thoracotomy used to access the heart involves trauma to the muscle tissue during removal of the fourth costal cartilage and a small piece of connected rib, perhaps leading to more severe postoperative pain compared with patients undergoing routine sternotomy. Intrathecal opioids can be used but have limited therapeutic duration and there is concern regarding anticoagulation. We present a case where soft tissue catheters were placed into the depths of the surgical wounds and pain was diminished greatly by intermittent regular infiltration with bupivacaine. (*Br. J. Anaesth.* 1998; **80**: 519–520)

Keywords: surgery, cardiovascular; heart, coronary artery bypass; anaesthetics local, bupivacaine

Case report

A 56-yr-old woman (height 154 cm, weight 94 kg, ASA IV) was referred for surgical management of coronary artery disease. Relevant medical history included chronic obstructive pulmonary disease, asthma, peptic ulcer disease and increasing angina. She underwent cardiac catheterization 2 months before with placement of a stent in the right coronary artery. However, angina recurred and she was referred for a minimally invasive direct coronary artery bypass (MIDCAB) procedure using a saphenous vein graft from the subclavian artery via a right anterior mini-thoracotomy approach to the right coronary artery.[1]

The patient was sedated and taken to the operating theatre. Standard monitors, including external defibrillation pads, were applied. A large bore i.v. catheter and right radial artery catheter were inserted. Anaesthesia was induced with sufentanil 1 $\mu g\ kg^{-1}$, etomidate and rocuronium. A left-sided, 37-French, double-lumen tracheal tube was inserted, and placement was confirmed with a fibreoptic scope. Anaesthesia was maintained with sevoflurane, propofol and oxygen. Nitroglycerin was used intermittently during the course of surgery. A pulmonary artery catheter was inserted after intubation. The patient was not placed on cardiopulmonary bypass during the course of the procedure.

An 8-cm incision was made over the right fourth costal cartilage. The surgeon dissected through subcutaneous fat, the pectoralis major and pectoralis minor to the perichondrium and periosteum of the fourth costal cartilage and rib. The rib was then mobilized by dissecting the intercostal muscles, and 3 cm of rib and costal cartilage were removed. The pericardium was opened, and the right coronary artery was identified. A second 8-cm incision was made exposing the right subclavian artery. After administration of i.v. heparin, the right coronary artery was bypassed using a saphenous vein graft from the subclavian artery. Before the surgical incisions were closed, irrigating catheters (Zimmer 7 mm × 20 cm) were placed in the soft tissues of both wounds for infiltration with bupivacaine after operation. The catheters were fully perforated flat silicon drains, cut so that the perforated part was 4–5 cm long. In the mini-thoracotomy incision, this was curled in position so that both soft tissues and nearby intercostal nerves were irrigated. In the subclavian incision, the perforations were arranged to irrigate soft tissue and muscle tissue traumatized in the approach to the subclavian and axillary arteries. The drainage tubes were then brought through tunnels to exit sites 6 cm from the surgical incision. A 0.2-µm antimicrobial filter (Arrow, Reading, PA, USA) was attached externally to minimize the risk of infection.

The patient was taken to the intensive care unit (ICU) in a stable condition and weaned from the ventilator over the following 4 h. Both soft tissue catheters were infiltrated with 20 ml each of 0.25% bupivacaine every 6 h. The catheters remained in place for approximately 48 h and were removed without adverse effects on the surgical wound. During the 48 h that the soft tissue catheters were in place, the patient received pethidine 40 mg, diazepam 2 mg and ketorolac 180 mg. After an uneventful postoperative course, the patient was discharged from hospital on the third day after operation.

Discussion

MIDCAB surgery is gaining acceptance as an adjunct to conventional coronary surgery in selected patients. Advantages include the potential for lower

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morbidity, shortened ICU and hospital stay, cost-effectiveness, avoidance of cardiopulmonary bypass and decreased surgical trauma to the chest wall.[2 3] However, our experience has been that MIDCAB patients have more postoperative chest wall pain compared with patients who have undergone sternotomy. This is probably related to dissection through the pectoralis and intercostal muscles, in addition to removal of the fourth costal cartilage and some rib. Given that these patients are given anticoagulant therapies during and, not uncommonly, before operation, often they are not good candidates for extradural or intrathecal pain management.

A clear goal with MIDCAB patients is a shortened operative time with early extubation, either in the operating theatre or within 4 h of arriving in the ICU. To achieve this end, it is necessary to have a patient with good respiratory function, clear cerebration, adequate warmth, minimal chest drainage, stable haemodynamics and minimal pain.[4] Non-opioid pain management provides an alert and co-operative patient while avoiding respiratory depression or excess sedation. Placement of a multi-porous catheter in the surgical wound worked well to achieve this goal in our patient. The patient experienced excellent analgesia with no side effects and was discharged from hospital within 72 h after operation.

This case in no way substitutes for a comprehensive study but suggests potential treatment for postoperative pain in patients undergoing MIDCAB surgery. The choice of local anaesthetic, concentration and volume were derived from studies on interpleural analgesia.[5 6] Further study is needed to clarify optimal anaesthetic type, concentration and volume. To avoid potential local anaesthetic toxicity, catheters are aspirated for signs of intravascular migration before injection, and the bupivacaine dose is limited to a maximum of 2 mg kg^{-1} every 6 h. Interpleural analgesia, which is distinct from our method, has been used effectively for several years to treat multiple rib fracture and cholecystectomy, thoracotomy, renal and breast surgery.[4-7] Our procedure shares similarities, but the local anaesthetic is placed closer to the surgical wound. We measured chest tube drainage after injection and no significant increase was noted. There are similar concerns regarding local anaesthetic toxicity and patients must be monitored for signs of central nervous system dysfunction, pneumothorax, pleural effusion and tamponade.

In summary, this wound irrigating catheter technique appears to be efficacious in providing postoperative pain control in patients undergoing MICAB surgery. It has the advantage of minimizing chest wall pain to improve the patient's chances of early tracheal extubation and discharge from the ICU. Further investigation with controls is being undertaken.

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EQUIPMENT

Error in measurement of oxygen and carbon dioxide concentrations by the DeltatracII metabolic monitor in the presence of desflurane

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Summary

In experiments in dogs on the metabolic effects of inhalation anaesthetics, we noticed that in the presence of desflurane, oxygen uptake ($\dot{V}O_2$) measured with the DeltatracII metabolic monitor seemingly increased whereas it decreased when determined independently by the Fick principle. This difference remained even after correction for changes in gas concentration on addition of an inhalation anaesthetic. Therefore, we suspected that desflurane interferes with the measurement of gas concentrations. Using different precision gases, we found that desflurane disturbed both the paramagnetic oxygen sensor and the infrared carbon dioxide detector so that the measured oxygen (when F_{IO_2} was >0.21) and carbon dioxide concentrations were greater than expected. These errors multiply in the computing process of oxygen uptake by the DeltatracII. When the DeltatracII is to be used during inhalation anaesthesia, its results should be corrected for the presence of an anaesthetic gas. More importantly, corrections must also be made for measurement errors of the oxygen and carbon dioxide sensors, unless the device has been equipped with a modified (nickel membrane) oxygen sensor insensitive to the presence of volatile agents. (*Br. J. Anaesth.* 1998; **80**: 521–524)

Keywords: anaesthetics volatile, desflurane; monitoring, oxygen; measurement techniques, calorimetry; equipment, gas analysers

We would like to draw attention to a source of error in the measurement of oxygen and carbon dioxide concentrations in the presence of inhalation anaesthetics in one particular analyser. The problem arose in experiments on the metabolic effects of desflurane in dogs. Using the DeltatracII metabolic monitor (Datex Instrumentation Corp., Helsinki, Finland) we noticed that both oxygen uptake ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) seemingly increased with increasing desflurane concentration whereas it decreased with other inhalation anaesthetics. This overt discrepancy was also surprising because cardiac output markedly decreased in association with only a slight increase in the arteriovenous oxygen content difference, regardless of the anaesthetic used, that is even in the presence of desflurane. To resolve these contradictory observations, we determined $\dot{V}O_2$ by the Fick principle (from the arteriovenous oxygen content difference and cardiac output), independently of the DeltatracII.

We found that these $\dot{V}O_2$ values were markedly lower than those measured by the DeltatracII, even after correction of the latter for dilution of the respiratory gases on addition of desflurane.[1] Hence the large concentrations of desflurane (MAC 6–7%) used for anaesthesia[2] and the subsequent greater inspiratory–expiratory desflurane difference alone did not entirely explain this considerable discrepancy. Therefore, we suspected that desflurane was causing an error in the measurement of gas concentrations, most likely by interfering with either the paramagnetic oxygen sensor (OM-101, Datex) or the infrared absorption carbon dioxide detector (CX-104, Datex), or both, used in the DeltatracII. This led us to evaluate the effects of desflurane on the measurement behaviour of both sensors in the presence of precision gases containing different concentrations of oxygen, carbon dioxide, or both.

Materials and methods

The DeltatracII is an open circuit indirect calorimeter using a gas dilution principle for determining respiratory gas volumes required for gas exchange measurements.[3] The paramagnetic oxygen sensor measures the difference in oxygen concentrations between inlet I (alternating inspired gas or room air) and inlet II (mixed expired gas) (fig. 1A). (Note that the microphone membrane of the differential oxygen sensor is made of plastic and covered with a metal layer (gold) at inlet I.) Unlike in standard gas analysers, in which the plastic surface of the sensor membrane (at inlet II) is exposed exclusively to air (fig. 1C), volatile anaesthetics may reach both sides of the sensor membrane in the DeltatracII (fig. 1A, B) and thus affect its sensitivity.

Before each experiment, the gas sensors were calibrated with a high precision gas (5.00±0.03% carbon dioxide–balance oxygen; Messer Griesheim, Duisburg, Germany) and the DeltatracII measurement of

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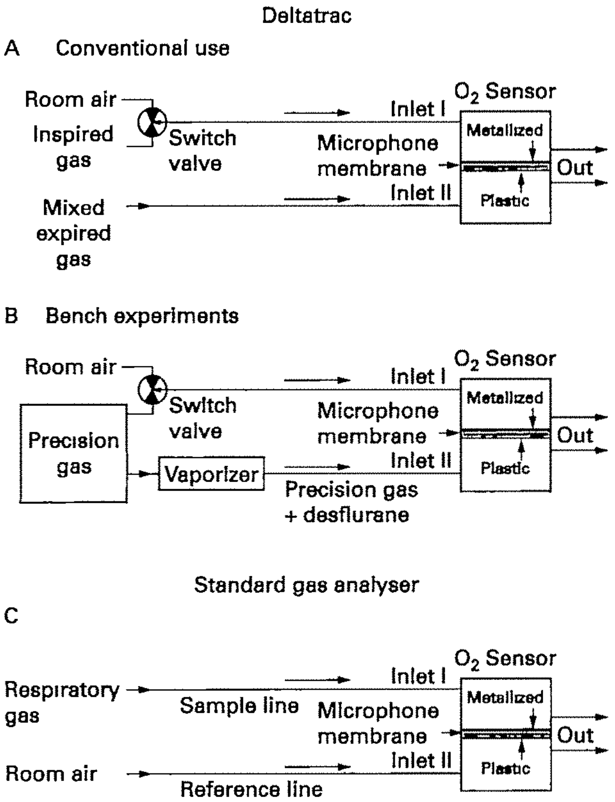

Figure 1 Schematic representation showing the oxygen measurement configuration in the DeltatracII metabolic monitor during conventional use (A) and during our bench experiments (B) compared with the configuration in standard gas analysers (C).

oxygen uptake was calibrated by burning ethanol 5 ml (99.9%, alcohol burning test kit of Datex).

In our bench experiments (fig. 1B), three precision gases (Messer Griesheim) containing various oxygen concentrations (20.9%, 30.3% or 50.1% oxygen–balance nitrogen) were sucked (flow = 100–150 ml min^{-1}) through the inspiratory port of the DeltatracII (inlet I) to the metallized side of the sensor membrane. The same gases, after equilibration with 0, 7 and 14 vol.% desflurane (vaporizer Tec 6, Ohmeda, Steeton, UK), were fed to the mixing chamber of the DeltatracII (at a flow of 2 litre min^{-1}) from where samples were sucked to the plastic side of the sensor membrane (via inlet II). In this way it was possible to recognize if the presence of desflurane at the plastic side of the oxygen sensor membrane (via inlet II) would disturb the oxygen concentration measurement of the inspiratory gas sample (inlet I). Desflurane concentrations were monitored continuously by infrared spectroscopy (Capnomac Ultima SV multi-gas analyser, Datex).

Results

With the sensor membrane exposed to desflurane via inlet II, the DeltatracII measured erroneously large oxygen concentrations of the inspiratory gas sample. This is shown by the relations between oxygen concentrations in the precision gases and those measured by the DeltatracII in figure 2A. As expected, in the absence of desflurane, the data points fell almost on the line of identity, indicating that the DeltatracII measured oxygen concentrations correctly in these circumstances. However, in the presence of desflurane at inlet II, the DeltatracII measured the oxygen differentials (i.e. $O_{2\ \text{sample gas}} - O_{2\ \text{Air}}$) correctly only with room air as a carrier gas but gave higher readings when the oxygen concentrations increased at inlet I. As a result, the relationships between measured and expected oxygen differentials retained their linearity but were tilted anti-clockwise (fig. 2A). While the intercepts of these relationships were negligible (0.2 for each curve), their slopes increased from 0.97 to 1.07 and 1.23 (at 0, 7 and 14 vol.% desflurane), and could be related, by first approximation, to the fractions of desflurane (F_{Desf}) (see inset in fig. 2A): slope = $1+1.9\times F_{\text{Desf}}$.

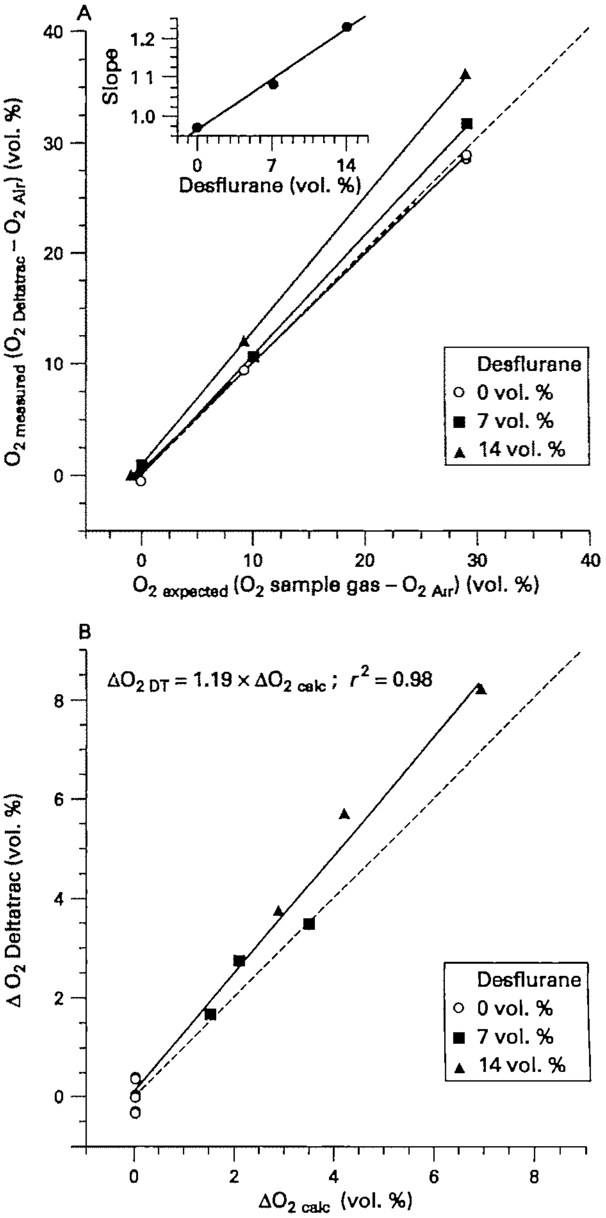

Figure 2 Effects of desflurane on measurements of oxygen concentrations. In A, measured oxygen concentrations deviated from those in the precision gases at larger oxygen and desflurane concentrations. Note that oxygen concentrations are measured against room air so that the difference becomes 0 when air is used as a carrier gas. The inset shows that the slopes of the resulting curves can be related linearly to desflurane concentrations, which alleviates correction. In B, the DeltatracII readings of ΔO_2 (i.e. oxygen concentration difference over the sensor membrane, inlet I *vs* II) were greater (19% on average) than expected in the presence of desflurane. The broken lines indicate identity.

Hence, it was possible to correct the oxygen measurements for this error:

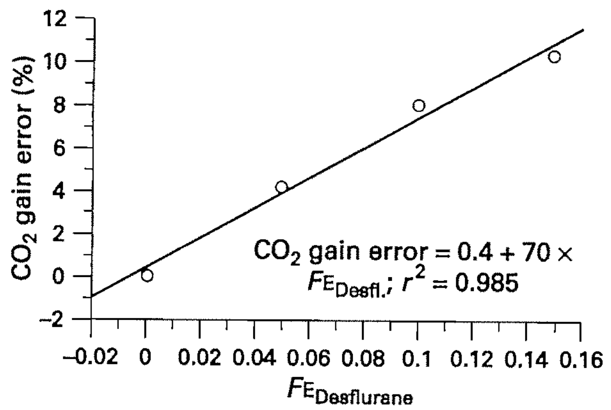

Figure 3 Effects of desflurane on measurements of carbon dioxide concentrations. The carbon dioxide gain error (% change in the ratio of measured and calculated carbon dioxide concentrations) and the desflurane fractions at inlet II ($F_{E_{Desflurane}}$) correlated linearly.

$$F_{O_2}^* = \frac{F_{O_2\,Deltatrac} - 0.209}{1 + 1.9 \times F_{Desfl}} + 0.209 \qquad (1)$$

where *indicates a corrected value and gas concentrations are given as fractions (*F*).

How this measurement error affects the inspiratory and expiratory oxygen concentration difference across the sensor membrane (i.e. ΔO_2 between inlet I and II) computed by the DeltatracII is shown in figure 2B. For the ranges of desflurane and oxygen concentrations studied, the data (ΔO_2, as measured by the DeltatracII=$\Delta O_{2\,Deltatrac}$ against ΔO_2, as calculated from dilution of the precision gases on addition of desflurane=$\Delta O_{2\,calc}$) fitted well a linear equation (see insert) with a slope notably steeper than the line of identity. Thus the DeltatracII readings were always greater (19% on average) than expected. This constant percentage error renders the correction of $\Delta O_{2\,Deltatrac}$ simple:

$$\Delta F_{O_2}^* = \frac{\Delta F_{O_2\,Deltatrac}}{1.19} \qquad (2)$$

Although of less importance, desflurane also disturbed the infrared carbon dioxide sensor. On addition of desflurane (5, 10, and 15 vol.%), measured carbon dioxide concentrations were 4.2, 7.8 and 10.4% greater than those calculated using a precision gas containing 5.00 ± 0.03% carbon dioxide–19% oxygen–76% nitrogen. Thus the gain error (% change in the ratio of measured and calculated values) increased linearly with desflurane fractions (fig. 3) and can be compensated for by the following equation:

$$F_{E_{CO_2}}^* = \frac{F_{E_{CO_2\,Deltatrac}}}{1 + (70 \times F_{E_{Desfl}} + 0.4)/100} \qquad (3)$$

where *F*E=expiratory gas fractions.

Finally, with the corrected gas concentrations, $\dot{V}_{O_2}$ can be calculated using a modification of the Haldane transformation for anaesthesia, as suggested by Aukburg and colleagues[1]:

$$\dot{V}_{O_2}^* = \left(F_{I_{O_2}}^* \times \frac{F_{E_{O_2}}^* + F_{I_{N_2}} + F_{E_{CO_2}}^* + F_{E_{An}}}{F_{I_{O_2}}^* + F_{I_{N_2}} + F_{I_{An}}} - F_{E_{O_2}}^*\right) \times \dot{V}_E \qquad (4)$$

where F_{O_2}, F_{N_2}, F_{CO_2} and F_{An} (anaesthetics) are the respective inspiratory (*F*I) and expiratory (*F*E) gas fractions, $\dot{V}_E$ is the expired minute ventilation under STPD conditions, and expressions marked by * indicate mean corrected values according to equations (1)–(3). Those terms which are not directly available at the data output string of the DeltatracII can be calculated according to $F_{E_{O_2}} = F_{I_{O_2}}^* - \Delta\ F_{O_2}^*$ and $F_{I_{N_2}} = F_{N_2} \times (1 - F_{I_{An}}) \cong F_{E_{N_2}}$ during steady state conditions.

In fact, as exemplified in table 1 for one dog, $\dot{V}_{O_2}$ values calculated by equation (4) agreed well with those obtained independently by the Fick principle (last column). Note also that in the presence of desflurane, the DeltatracII readings (first column), even when corrected for the presence of anaesthetic gases (second column), yielded $\dot{V}_{O_2}$ values which were up to 1.7 and 1.3 times greater than the reference method (Fick, last column). Similar results were obtained in 10 experiments on six dogs (data not shown).

As the $\dot{V}_{O_2}$ measurements by the Fick principle were used as a reference, we took care to measure as accurately as possible both the arteriovenous oxygen content difference and cardiac output. Arterial (carotid artery) and mixed venous blood (pulmonary artery) were sampled simultaneously in air-free syringes and the total oxygen content in blood measured immediately in duplicate (Lex O_2 Con, Lexington Instr., Waltham, MA, USA).

Cardiac output (i.e. pulmonary blood flow) was measured continuously (beat by beat) with ultrasonic transit-time flow probes (Transonic, Ithaka, NY, USA) chronically implanted around the pulmonary artery (after approval by the local District Government) and averaged over the entire blood sampling period.

For every measurement, we calculated the worst case error according to the law of error propagation: the accuracy of the oxygen content analyser is ±1% for a single measurement and ±0.75% for the mean of two measurements. Hence the 95% confidence interval for an arterial or mixed-venous sample is within ±1.5% (± 2 SD) of the measured value and the error of the calculated arteriovenous oxygen content difference sums up to 6% (2×3%).

The accuracy of the ultrasound transit-time flowmeter is ±7.5% for a single stroke volume but improves to ±1.2% (7.5 √40) by averaging over the sample period (i.e. approximately 30 s or 40 beat min⁻¹). The resultant maximum errors of the $\dot{V}_{O_2}$ values determined by the Fick principle (the product of

Table 1 Effects of desflurane on measurements of oxygen (O_2) uptake. O_2 uptake is shown as measured by the DeltatracII before and after corrections and as the reference values determined by the Fick principle. Data from one representative experiment in a dog

	O_2 uptake (ml kg^{-1} min^{-1})			
Desflurane (vol. %)	Original DeltatracII readings	Corrected according to Aukburg and colleagues[1]	Corrected according to eqn (4)	Determined by the Fick principle
0	4.3	4.3	4.3	4.3
7	4.6	4.1	3.6	3.6
14	5.1	4.0	3.2	3.1

arteriovenous oxygen content difference and cardiac output) add to 9 and 10% (at 7 and 14 vol.% desflurane), which is acceptable in view of the 28–65% deviation of $\dot{V}O_2$ values obtained by the DeltatracII.

Of note, lung oxygen consumption, which is not detected by the Fick measurement but is detected with the DeltatracII, is less than 5% of total $\dot{V}O_2$ and thus negligible in healthy dogs and humans.[4 5]

Discussion

Desflurane disturbed, in a concentration-dependent manner, measurements of oxygen and carbon dioxide concentrations in the DeltatracII metabolic monitor. As a consequence, the oxygen concentration differences across the sensor membrane (inspiratory to expiratory ΔO_2) were overestimated by approximately 20% in the presence of desflurane. As ΔO_2 is a dominant factor in the computation of $\dot{V}O_2$ ($\dot{V}O_2 = \Delta O_2 \times \dot{V}E$), erroneous increases in ΔO_2 must also yield erroneous increases in $\dot{V}O_2$. In fact, the DeltatracII yielded $\dot{V}O_2$ values which were up to 1.7 times greater than expected (Fick principle) (table 1) if no corrections were applied. Hence the DeltatracII readings must be corrected for both the addition of desflurane (which alters respiratory gas concentrations) and also for the error in the measurement of gas concentrations. The correction for the first problem according to Aukburg and colleagues[1] yielded $\dot{V}O_2$ values that were up to 30% greater than the Fick values. This discrepancy reflects the error in the measurement of gas concentrations because it was eliminated by the appropriate corrections using equations (1)–(4), as evidenced by the agreement of the corresponding $\dot{V}O_2$ values with the reference (see last two columns in table 1).

The measurement errors of the gas sensors are not unique to desflurane, as we have found that other inhalation anaesthetics disturbed the oxygen and carbon dioxide detectors in a similar manner (data not shown). Yet because of the smaller concentrations used for anaesthesia, impairment of gas concentration measurements matters little for the computation of $\dot{V}O_2$.

Interference of volatile anaesthetics with carbon dioxide detectors has been reported previously,[6] the underlying mechanism being deformation of the infrared carbon dioxide absorption peak by collision of carbon dioxide with other gas molecules.[7] However, this carbon dioxide measurement error is of minor relevance for calculation of $\dot{V}O_2$ as its correction alone decreased the $\dot{V}O_2$ readings of the DeltatracII by only 1–2%.

We have shown for the first time that volatile anaesthetics (which are non-paramagnetic molecules) also disturb the paramagnetic oxygen sensor. The culprit for this error seems to be the plastic surface which alters the sensitivity of the microphone membrane of the differential oxygen sensor either by deformation of its thickness (swelling) or change of its dielectric constant as desflurane is absorbed. Consistent with this view, replacing the plastic membrane by one made from nickel almost completely eliminated the oxygen measurement error induced by desflurane (data not shown). Standard gas monitors which use the same gas sensors (e.g. the Capnomac Ultima, Datex) were not affected by desflurane because the plastic surface of its microphone membrane is always exposed to room air thus preventing contact with volatile agents (fig. 1c).

Of note, the DeltatracII metabolic monitor has not been designed for metabolic studies during inhalation anaesthesia. Nevertheless, it can be used for this purpose when the appropriate corrections are made for the changes in respiratory gas concentrations by additional gases and, in particular, for the effects of inhalation anaesthetics on the measurement of gas concentrations, as we have shown. Another option would be to use gas sensors which are not disturbed by volatile anaesthetics. Such modified sensors will be available soon as spare parts for the DeltatracII metabolic monitor. The new version of the paramagnetic oxygen sensor of the Datex-Engstrom,[8] as implemented in the compact gas exchange module M-COVX of the Datex AS/3 monitor system, is equipped with a nickel film microphone membrane and therefore is immune to volatile anaesthetic agents.

It should be noted that the DeltatracII cannot be used during anaesthesia with nitrous oxide instead of nitrogen. In this case, the Haldane transformation used to derive inspired from expired tidal volumes does not apply because of the different uptake kinetics of nitrous oxide. Furthermore, it should be remembered that our corrections apply to steady state conditions rather than to rapidly changing gas concentrations, and that different gas sensors may require an individual check of its correction factors. Finally, it is a pleasing result that oxygen uptake, when determined correctly, does not increase, but rather decreases in the presence of desflurane, in common with other inhalation anaesthetics.[9]

Acknowledgements

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British Journal of Anaesthesia 1998; **80**: 525–527

Video-intuboscopy: a new aid to routine and difficult tracheal intubation

M. Weiss

Summary

Video-intuboscopy gives a video display of the view from the tip of the tracheal tube during conventional laryngoscopy, and was developed particularly to assist the immediate management of unexpected difficult intubation. A lightweight, malleable video-optical intubation stylet transmits the view from the stylet tip onto a monitor. It is inserted in the tracheal tube before starting anaesthesia, and the view from the tracheal tube tip enables the anaesthetist to verify tracheal tube position in the trachea. During difficult intubation the video view is used to guide the tracheal tube into the trachea. When used to allow confirmation of tracheal placement, the system did not interfere with conventional intubation procedures. The method showed the subglottic airway, gave immediate confirmation of tracheal tube position, and aided teaching and supervision. The method was used to guide intubation in two patients with unanticipated grade 3 laryngoscopic views. Intubation was simple, rapid and atraumatic, without the need for head, neck or laryngeal manipulation. Tracheal placement was instantly confirmed using the video view from the stylet tip. Clinical studies are required to define the value of this new intubation technique. (*Br. J. Anaesth.* 1998; **80**: 525–527)

Keywords: anaesthetic techniques, laryngoscopy; larynx, laryngoscopy; intubation tracheal, difficult; intubation tracheal, technique; equipment, video-endoscope

Difficult tracheal intubation is an important cause of morbidity and mortality in anaesthesia.[1] Unexpected difficult intubation is a major cause of anaesthetic misadventure.[2] The most common factor preventing successful tracheal intubation is the inability to see the vocal cords during direct laryngoscopy.[3] To overcome the obstructed view to the glottic opening, many devices are designed to look "around the corner", such as mirror and prism laryngoscopes, fibrebronchoscopes, optical intubating stylets and optical intubating laryngoscopes.[4-8]

I describe a new intubation technique, intended primarily as a technique to confirm tracheal intubation, which allows immediate and safe management of unexpectedly difficult direct laryngoscopy. The principle of this new approach is tracheal tube guidance by viewing the vocal cords using the video view from the tracheal tube tip. Therefore, I designed a malleable video-optical intubation guiding stylet, to transmit the video view from the stylet tip directly to a video monitor. This enables the anaesthetist to guide the tracheal tube between the vocal cords into the trachea under video visual control.

Video display of the view from the tracheal tube tip during conventional laryngoscopy is termed "video-intuboscopy".

Materials and methods

INSTRUMENTATION

The device (fig. 1 (top)) consists of a thin, malleable, metallic-forming element and an ultra-thin fibreoptic element (Video-microbendoscope, Volpi AG, Schlieren, Switzerland), bound together by a plastic tube to form a lightweight intubation stylet. The proximal end of the stylet carries a connector that fits to the 15-mm tracheal tube adapter. The video-microbendoscope leaves the proximal stylet as a 2-m long transmitting cable, which is attached by the proximal plug to a compact video camera–light source unit (Intralux Video Compact, Volpi AG, Schlieren, Switzerland). The video-microbendoscope carries optic fibres for image transmission (10 000 pixels) from the stylet tip to the video camera unit and additional light fibres for airway illumination. It is re-usable and can be sterilized using ethylene oxide.

The video-optical stylet is inserted into a tracheal tube (fig. 1 (bottom)) and locked with the stylet connector to the tracheal tube adapter, preventing rotational and longitudinal displacement. The stylet tip slightly protrudes the tracheal tube tip. Using the internal forming element, the tracheal tube can be bent to the required shape.

TECHNIQUE

Standby mode (confirmation of tracheal intubation)

The stylet is inserted in the tracheal tube and checked for correct view and function before starting anaesthesia. After induction of anaesthesia with thiopental 5 mg kg^{-1} and neuromuscular block with pancuronium 0.1 mg kg^{-1}, anaesthesia is maintained with 2% sevoflurane and 65% nitrous oxide in oxygen by mask ventilation. Conventional direct laryngoscopy is performed and the trachea is intubated under direct vision as usual. After the tracheal tube tip has passed the vocal cords, the laryngoscopist uses the

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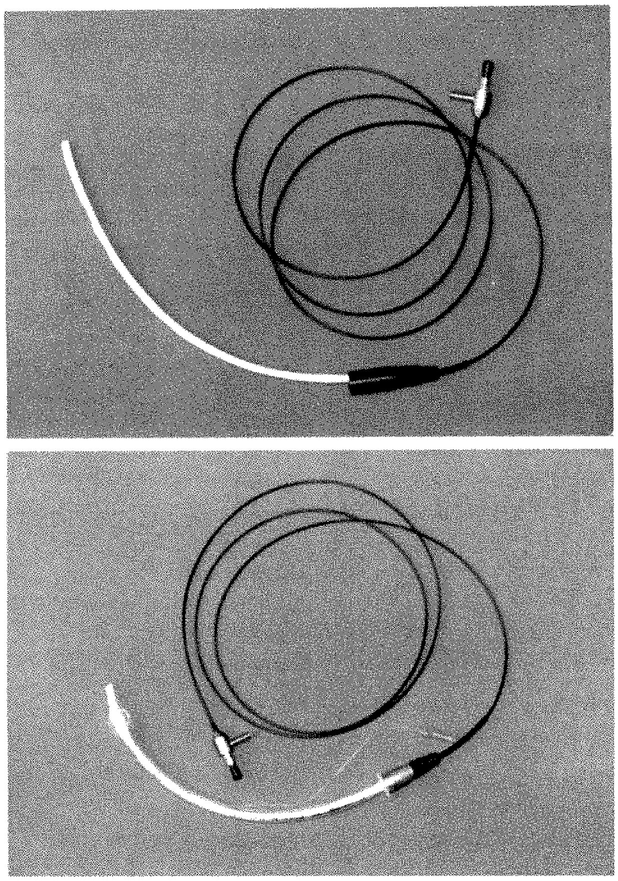

Figure 1 Malleable, video-optical intubation stylet (od 5 mm) with proximal tracheal tube (TT) connector, 2 m of transmitting cable (od 2.3 mm) and video camera–light source (top). TT (id 7.5 mm) loaded with the video-optical intubation stylet (bottom).

video display to confirm tracheal tube position and adjust the tracheal tube as required using the video view transmitted from the stylet tip. The video-optical stylet is then removed from the tracheal tube.

Intubation mode (guided tracheal intubation)

If a view of the vocal cords cannot be obtained during tracheal intubation, the best possible direct laryngoscopic view is maintained with the laryngoscope blade in one hand. The tracheal tube loaded with the video-optical intubation stylet is introduced into the oropharynx with the other hand. The anaesthetist then uses the video view from the tracheal tube tip to guide the pre-formed tracheal tube between the vocal cords and into the trachea, and confirm the correct position, before the stylet is removed.

FIRST EXPERIENCES

Standby mode (confirmation of tracheal intubation)

Six operators used the video-optical intubation stylet in 30 patients undergoing elective surgery, and reported no disadvantages. The low weight, malleable nature and thin, flexible, transmitting cable to the video camera–light source unit allowed the video-optical intubation stylet to be used in the same way as a conventional intubation stylet. Removal of the video-optical intubation stylet was uneventful and any time delay from stylet removal was no longer than that with conventional gum elastic bougies or intubation stylets.

Intubating mode (guided tracheal intubation)

Intubation was guided in two patients with unexpected difficult laryngoscopy (grade 3 view).[9] In the first patient the video-optical intubation stylet was already loaded in the tracheal tube (standby mode) so that the anaesthetist had only to change his view to the video-display and tracheal intubation was carried out under video visual control within another 15 s. In the second patient, after initial direct laryngoscopy without intubation attempts, mask ventilation was performed for a short period to prepare the tracheal tube with the video-optical stylet. The patient was then intubated within 30 s with another conventional laryngoscopy and using the video-view from the tracheal tube tip.

In both patients intubation was performed successfully at the first attempt, in a rapid and safe manner, each by a different anaesthetist with no previous experience of this method. There was no need for head, neck or laryngeal manipulation, or help from an assistant.

Discussion

REVIEW

Video-intuboscopy is a new indirect laryngoscopic intubation technique and combines the three following elements: (1) intuboscopy (transmission of the view from the tracheal tube tip to a proximal viewfinder), (2) conventional laryngoscopy and (3) video-endoscopy.

Intuboscopy

Intuboscopic-guided intubation was first described by Murphy in 1967.[10] He used a fibreoptic choledoscope in a nasally passed tracheal tube. Both tracheal tube and flexible endoscope were advanced together and steered into the trachea by twisting the proximal tracheal tube while watching through the viewfinder.[10]

Conventional laryngoscopy

Conventional direct laryngoscopy combined with fibrebronchoscopic intubation in anaesthetized patients, performed by two anaesthetists, has been reported as a useful intubation technique, providing enough room in the pharynx for steering the endoscopic instrument to the vocal cords, particularly if the pharynx is obscured by copious secretions, blood or soft tissue swelling.[11]

Video-endoscopy

Video-endoscopy implies that the anaesthetist does not have to look into an eyepiece, and facilitates endoscopic procedures.[12] The video display aids dexterity and enables nearly simultaneous observation of the video monitor, patient and monitors in a comfortable and efficient position for intubation.

Video-endoscopy for tracheal intubation is used mainly for demonstrating and teaching direct laryngoscopy, fibrebronchoscopy or the Bullard intubation technique.[12-15]

VIDEO-INTUBOSCOPY

Standby mode

The video-optical stylet provides a useful means of monitoring tracheal tube position, and teaching and supervising tracheal intubation.

Airway monitoring. Airway imaging allows accidental oesophageal intubation to be detected and avoids endobronchial intubation during the intubation procedure.[16] Furthermore, subglottic airway pathology such as laryngeal or tracheal tumours, stenosis, compression, webs or an aberrant tracheal bronchus could be detected during intubation, so that airway management may be modified appropriately. The costs for a compact video-intuboscopic imaging unit ($6000) are relatively low compared with median payments for claims for respiratory adverse events ($200 000) and are in the range of other anaesthetic monitoring equipment.[17] Further development of the device to provide a disposable guide and covering element, containing the reusable fibreoptic part, would allow it to be used as a cost effective device.

Teaching direct laryngoscopy is usually limited because the instructor cannot see the view of the laryngoscopist during the procedure. Headframe-mounted video camera systems and video transmission from the laryngoscope blade have been developed for video visualization direct laryngoscopy.[13,18] Video-intuboscopy in the "standby mode" is another means of allowing demonstration, teaching and supervising of intubation using the video view from the tracheal tube tip.

Intubating mode

Limited experience (in two patients with grade 3 laryngoscopy) indicated that video-intuboscopic-guided tracheal intubation can allow simple, rapid, safe and gentle intubation. Looking at a video-display in critical circumstances is much more comfortable than looking into a viewfinder of an endoscopic device, because the operator remains in the usual intubation position and can change the view from the oropharynx to monitor and vice versa. Teaching and supervising is facilitated with the video monitor.

Most anaesthetists are skilled in conventional laryngoscopy and in steering an intubation guiding stylet. Video-intuboscopic-guided tracheal intubation is almost the same procedure, except that the tracheal tube is guided by the video view from the stylet tip. This makes the video-optical intubation stylet an easy device to handle.

If the device is being used to confirm intubation, when a patient is encountered with unpredicted difficult intubation, the method can be changed promptly to aid intubation. There is no delay in preparing intubation equipment, no need to interrupt the intubation procedure and no need for additional help.

The method may be beneficial in patients with cardiovascular diseases, dental disorders and in patients with cervical spine pathology. However, these possibilities need to be confirmed by further investigations.

Difficult tracheal intubation complicated by oropharyngeal secretions, swelling and bleeding, in which fibrebronchoscopic intubation may fail, could be managed by simultaneous direct laryngoscopy and video-intuboscopic-guided intubation, as has been done with fibrebronchoscopes.[11,19] Lifting the tongue with the blade enables suction with large bore catheters and provides enough pharyngeal room for direction of the tracheal tube into the glottic opening.

Training in video-intuboscopic-guided intubation may be obtained by simulating difficult intubation.[19,20] This would allow initial direct laryngoscopy and video-guided tracheal intubation while lowering the laryngoscope blade so that the epiglottis descends and conceals the cords. In this way, training in video-intuboscopic-guided intubation can be done without jeopardizing patient safety and without loss of experience in direct laryngoscopic intubation.

Clinical studies are required to confirm simplicity and efficacy, to define the further role and to explore other applications of this new intubation technique.

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CITATION CLASSIC

Commentary

Ali HH, Utting JE, Gray C. Stimulus frequency in the detection of neuromuscular block in humans. *British Journal of Anaesthesia* 1970; 42: 967–978.

Before 1970, neuromuscular block in humans was measured either as responses to single nerve stimuli or to brief tetanic trains. Neither method was entirely satisfactory: return of a normal twitch response does not indicate full recovery and the use of tetanic stimulation is painful. Ali, Utting and Gray's article was a major advance. They wished to develop an objective quantifiable measurement of block. They examined responses to stimulation at various frequencies and to four stimuli given at 0.5-s intervals–the train-of-four. In volunteers and in patients with partial block produced by a non-depolarizing drug, they found that contractions were diminished at faster twitch rates and that fade was apparent with the train-of-four. In patients given succinylcholine, fade was not seen unless halothane was a component of the anaesthetic. In two subsequent articles,[1 2] they confirmed that the train-of-four ratio (the force of the fourth contraction as a fraction of the first of the train) was an objective index of recovery. They also claimed that with a train-of-four ratio of 0.6, head lift was possible. Thus they produced a tool to help both investigators of neuromuscular blocking drugs and clinicians. Later, Lee and Katz[3] added a derived measure–the train-of-four count. This is useful early in recovery from larger doses of neuromuscular blocking agents where the train-of-four ratio is zero.

The explanation for fade is still problematical. The popular notion is that non-depolarizing agents have a presynaptic action to diminish the release of acetylcholine. Normally it is thought that each release of acetylcholine acts in part presynaptically to improve mobilization of subsequent quanta. Without this, there is a run-down in the availability of transmitter. But there is a problem. The presumed presynaptic receptors must be very close to the postsynaptic receptors. There are no obvious anatomical barriers for the blocking drug to reach either receptor. Therefore, fade ought to develop as quickly as twitch block. It does not. There is more fade at a given level of twitch block during recovery than during onset.[4] Also, the successors at Liverpool, while able to produce a pharmacodynamic model for the first and fourth twitches, could not produce one for the ratio.[5 6] There must still be more to come to account for this hysteresis.

After Ali, Utting and Gray's[2] proposal that a train-of-four ratio of 0.6 would be associated with normal muscle function, there has been a move towards 0.7 as the ratio at which no previously paralysed patient should be left to his own devices. This is partly because of the difficulties in deciding if a palpated or observed ratio is greater than 0.7.[7] (If there is a measured EMG, a force or an acceleration monitor, the question does not arise.) The problem is psychological in that one has to remember the strength of the first contraction, ignore the responses to the second and third, and then compare the fourth with the first, and all within 1.5 s! I do not think our short-term memories can cope well with this challenge. Engbaek, Ostergaard and Viby-Mogensen[8] introduced an easier test, double-burst stimulation. This is a reversion to using very brief tetanic stimuli with two trains. It is easier to assess.

There is one additional problem. Kopman, Yee and Neuman[9] have recently examined again the train-of-four in conscious volunteers who were partially paralysed. Using infusions of mivacurium to maintain a set train-of-four ratio, all subjects reported feeling weak and not being "street ready" at ratios of 0.7. Their recommendation is that we should take 0.9 as the desirable end-point.

But the introduction of train-of-four monitoring was a noteworthy achievement. After its introduction, neuromuscular block was monitored more often and assessed better. Together with the introduction of shorter duration drugs, neuromuscular block has been achieved and maintained more easily. Ensuring an absence of fade leaves patients more able to cope.

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Brit. J. Anaesth. (1970), **42**, 967

STIMULUS FREQUENCY IN THE DETECTION OF NEUROMUSCULAR BLOCK IN HUMANS

BY

HASSAN H. ALI, J. E. UTTING AND CECIL GRAY

SUMMARY

Study of the literature on the physiology of neuromuscular transmission suggested two new methods of assessing the degree of neuromuscular block in the human subject. These were, first, a comparison of the height of the recorded twitch tensions developed in response to repeated single stimuli applied at differing frequencies and, second, examination of the extent of reduction in amplitude of twitch tensions developed in response to a short train of four stimuli. In assessing the first method the use of three frequencies of stimulation was tried (i.e., 0.1 Hz (c.p.s.), 0.3 Hz and 1.0 Hz). It was found that as the frequency of stimulation was increased there was reduction in the amplitude of the recorded twitch response in curarized subjects, and that this reduction appeared to depend on the degree of curarization. In assessing the second method a short train of four stimuli at 2 Hz was used, and it was found that there was a progressive fade of successive recorded mechanical twitch responses in curarized subjects which again appeared to depend on the degree of curarization. It is suggested that the amplitude of the twitch response at a higher frequency expressed as a percentage of that at the slower rate, and the last response of the train of four expressed as a percentage of the first may be useful in measuring degree of neuromuscular block in man.

It has been found that measurement of the force of an isometric muscle contraction evoked by motor nerve stimulation gives a more accurate index of neuromuscular block than does measurement of the action potential which is associated with the contraction (Botelho, 1955): indeed measurement of the force of contraction in this way has been said to be the best method of assessing neuromuscular block in clinical situations (Katz, 1965).

Study of the twitch response in a variety of conditions has shown that after administration of tubocurarine, and a number of other compounds the faster the rate of stimulation used the greater is the degree of neuromuscular block and the smaller will be the amplitude of the muscle twitch response obtained (Chou, 1947; Guyton and Reeder, 1949; Preston and Van Maanen, 1953; Wislicki, 1958; Blackman, 1963).

The decrease in the size of the muscle twitch which follows an increase in the stimulus frequency is rapid, a steady level usually being reached by the fifth twitch after changing to the faster rate when working in the range from 0.1 Hz to 10 Hz (Rosenblueth and Morison, 1937; Maaske, Boyd and Brosnan, 1938; Blackman, 1963).

Grob, Johns and Harvey (1956) demonstrated the effect of intra-arterial injection of various drugs on the evoked electromyogram in human subjects. They applied a standard pattern of stimulation which consisted of trains of four stimuli at a frequency of 25 Hz, the trains of stimuli being repeated at intervals of 2–10 seconds (i.e., 0.5–0.1 Hz). Before tubocurarine was given each of the four muscle action potentials obtained in this way was of equal height; and when a small dose of the drug (0.15 mg) was administered intra-arterially there was usually no effect on the initial muscle action potential of the train when it was compared with the pre-injection height. In these circumstances, however, there was slight steplike depression of the subsequent second, third and fourth potentials, the fourth being depressed most and the second least. As the dose of tubocurarine

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was increased depression of the first potential was also seen, together with increasing steplike depression of the successive three potentials, the fourth again being the most affected.

Roberts and Wilson (1968) have already used a train of four stimuli at 4 Hz to assess the progress and treatment of patients with myasthenia gravis. Evidence obtained in experimental animals and humans indicates that during repetitive nerve stimulation there is a progressive decrease in the amount of acetylcholine released from the motor nerve endings, a decrease reflected in a progressive decrease in the size of the endplate potentials (Liley and North, 1953; Boyd and Martin, 1956; Brooks and Thies, 1962; Elmqvist and Quastel, 1965).

The following investigation was undertaken in an attempt to find a satisfactory objective measure of changes of neuromuscular block based on these phenomena.

METHODS

Stimulation and recording.

The ulnar nerve was stimulated by means of 25-gauge needle electrodes placed subcutaneously at the wrists (Katz and Wolf, 1964). Mechanical twitch responses were elicited with square wave stimuli of 0.3 msec duration, the voltage being adjusted to 10–20 per cent above that required for maximal response. Stimuli were delivered through a stimulus isolation unit (Grass; SIU 478) from a Grass stimulator (model S8). The resulting adduction of the thumb activated a tensile/compressive transducer (Ether UFI ± 32 ounces), assembled in the form of a hand grip (Ali, 1970). This resulted in an almost completely isometric contraction. The output of the transducer was amplified and recorded on a Devices single channel recorder (type R2).

Pattern of nerve stimulation.

Single stimuli of duration 0.3 msec were delivered repetitively at frequencies of 0.1 Hz (one stimulus every 10 sec), 0.3 Hz (one stimulus every 3 sec) and 1 Hz (one stimulus every sec). In addition a train of four stimuli was delivered at a frequency of 2 Hz and a train duration of 2 sec (there was thus an interval of 0.5 sec between each of the four stimuli in the train); this train of four stimuli was repeated every 10 sec (i.e., at a train frequency of 0.1 Hz).

Ratios of twitch height.

Three ratios of twitch heights were selected for particular study. First the amplitude of the twitch at the highest frequency of stimulation (1.0 Hz) was expressed as a percentage of the amplitude obtained at the slowest rate of stimulation (0.1 Hz). Secondly, the percentage of the amplitude of the muscle twitch obtained when the frequency of stimulation was 1.0 Hz compared to the amplitude of the muscle twitch obtained at the frequency of 0.3 Hz. Thirdly, the height of the last of the train of four responses was expressed as a percentage of the height of the first response. These three ratios were considered as possible indices of the degree of recovery from the effect of the curarizing drug during surgery, and of the degree of residual curarization after neostigmine had been given. A group of conscious volunteers was also studied for the purpose of comparison.

Patients and volunteers.

Four groups of experiments were conducted, there being ten individuals in each group; in no case was there any evidence of neuromuscular disease. The age of the volunteers and patients was within the range of 18–65 years; the anaesthetized patients (groups 2–4 inclusive) were all undergoing elective lower abdominal or limb surgery.

Group 1 consisted of conscious volunteers. After a recording of the muscle response to the three different frequencies and to the train of four stimuli had been obtained for control purposes each volunteer was given tubocurarine 5 mg intravenously. The various patterns of stimulation were investigated until there was full recovery of the height of twitch responses to the control levels. The findings were correlated with the response to simple clinical tests for muscle paralysis.

Group 2 consisted of anaesthetized patients to whom a small dose of tubocurarine was administered; pulmonary ventilation was not controlled. Morphine 10 mg and atropine 0.6 mg was given as premedication 1 hour before surgery. Induction of anaesthesia was with thiopentone (200–300 mg) and was maintained with nitrous oxide and oxygen (5 l./min and 2 l./min) together with halothane (0.5–2 per cent). In some cases a face mask was used but in others an endotracheal tube was passed; in the latter case the larynx and trachea were previously anaesthetized with lignocaine solution (4 per cent). When a clinically steady state of anaesthesia had been achieved, each patient was given tubocurarine 10 mg: 15 min after the drug had been administered atropine 0.6 mg and neostigmine 2.5 mg were given to reverse the neuromuscular block. As in the volunteers in group 1, twitch responses were studied using the pattern described in the section on methods. Control heights of muscle twitch were obtained before the relaxant was given but after the patient had been anaesthetized, and the investigation was continued until full recovery of the twitch heights was achieved as compared to the control. The procedure was regarded as monitoring neuromuscular block and formal permission of the patient was not considered to be required; a full explanation of the procedure, however, was given to each patient.

Group 3 consisted of a group of anaesthetized patients to whom a larger dose of tubocurarine was administered; pulmonary ventilation had to be controlled. The premedication used was similar to that in the previous group, as was the induction of anaesthesia. The induction dose of thiopentone, however, was followed by tubocurarine 0.6 mg/kg body weight. A cuffed orotracheal tube was passed; anaesthesia was maintained with a mixture of nitrous oxide and oxygen 5 l./min and 2 l./min and IPPV was employed. No other supplement to the anaesthesia was used. At the end of the operation atropine 1.2 mg and neostigmine 5.0 mg were given together intravenously, either as a single dose or in two equal parts. Sometimes control values were obtained before the relaxant was given; in some cases, however, this was not done and the pattern obtained before neostigmine administration was used to compare with that obtained after the drug had been given.

Group 4 consisted of anaesthetized patients to whom suxamethonium was given. Premedication and the induction and maintenance of anaesthesia was similar to that used in the patients in group 3, and pulmonary ventilation was controlled until adequate spontaneous ventilation returned. The suxamethonium was given in a dose of 20–65 mg soon after the induction of anaesthesia and was used to facilitate endotracheal intubation. The effect of suxamethonium was also tested in patients after prolonged anaesthesia with nitrous oxide/oxygen and halothane (1–2 per cent); again controlled respiration was employed after suxamethonium was given, until adequate spontaneous respiration returned. The twitch response was studied before suxamethonium was given and during and after recovery from the drug.

RESULTS

The sections which follow give a qualitative account of the results obtained. A further paper (Ali, Utting and Gray, 1971) gives a quantitative account of the use of the train of four stimuli in assessing degree of residual curarization. It was found that the use of the train of four stimuli had advantages over the use of the simple change of frequency for the quantitative estimation of non-depolarizing block; for though the two indices ran pari passu the train of four stimuli appeared to be a more sensitive index.

Control tracings (all groups).

(a) *Change of frequency of stimulation.*

Before a muscle relaxant was given there was no diminution of the height of the twitch response following a change from lower to higher frequency (figs. 1, 2, 6, 7): this applied when the stimulus frequency was increased both from 0.1 Hz to 1 Hz and from 0.3 Hz to 1 Hz.

(b) *Train of four stimuli.*

In every case in which the train of four stimuli was applied before a muscle relaxant was given the twitch responses corresponding to each of the four stimuli were all of equal height (figs. 3, 5, 9, 10).

Pattern after tubocurarine (groups 1–3).

The change in the pattern of twitch response seen after tubocurarine was similar in the three groups in which its action was tested. The differences in the three groups were only in the degree of change observed.

(a) *Change of frequency of stimulation.*

A change in frequency of stimulation from 0.1 Hz to 1 Hz and from 0.3 Hz to 1 Hz caused a diminution of twitch height but the degree of depression was much more marked in the change from 0.1 Hz to 1 Hz; this change of frequency,

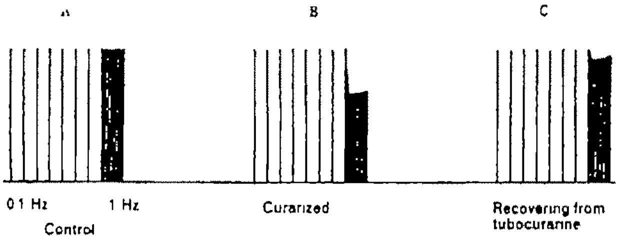

FIG. 1

Diagrammatic illustration of the effect of a small dose of tubocurarine on the twitch height obtained at two frequencies of ulnar nerve stimulation, 0.1 Hz (c.p.s.) and 1.0 Hz.

(A) Control muscle twitch before tubocurarine is administered shows no difference in twitch heights at the two rates of stimulation used.

(B) During curarization there may be initially no difference in the twitch height at the slower rate of stimulation from that obtained in the control period but a change to the faster frequency results in a sharp decline in twitch height.

(C) As recovery progresses the ratio of the twitch height at the faster to the slower frequency gradually approaches unity.

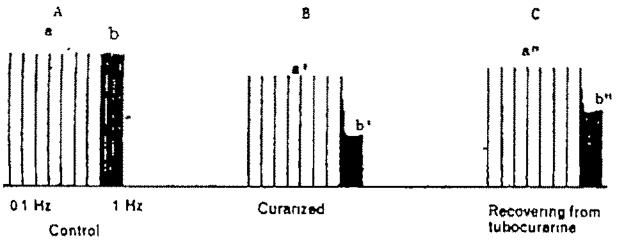

FIG. 2

A similar situation to that shown in fig. 1, but here the twitch heights at the lower rate of stimulation have been depressed. Note ratio b′/a′ is less than ratio b″/a″ and ratio b″/a″ is less than ratio b/a.

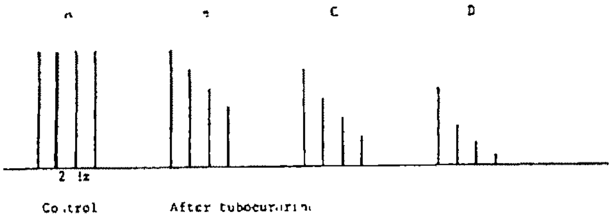

FIG. 3

Diagrammatic illustration of the effect of a small dose of tubocurarine on the isometric muscle twitch response to a train of four stimuli at 2 Hz.

A shows the control response; B, C, and D represent various degrees of curarization.

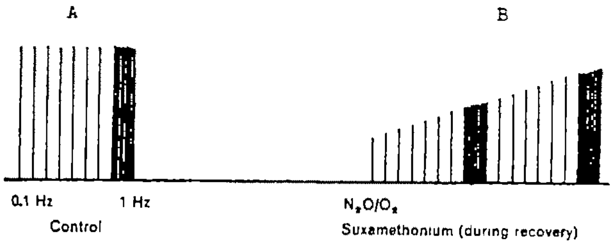

FIG. 4

Diagrammatic illustration of the effect of a small dose of suxamethonium (nitrous oxide/oxygen anaesthesia). When the evoked muscle twitches reappear after complete ablation change from slower to faster frequency does not change the slope of the recovery curve. (A) control; (B) during recovery from suxamethonium block.

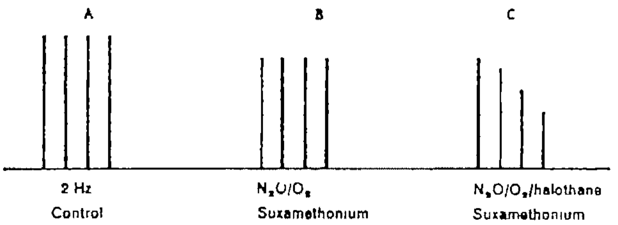

FIG. 5

Diagrammatic illustration of the effect of the administration of suxamethonium on the muscle twitch response to the train of four stimuli at 2 Hz.

A represents the control response (i.e., before the administration of the drug). Under anaesthesia with nitrous oxide and oxygen, suxamethonium reduces the twitch height in each of the four responses equally (B). Under prolonged halothane anaesthesia, however, a degree of fade was sometimes apparent after suxamethonium was given (C).

therefore, seemed to give a more sensitive index of the degree of curarization. In the figures attention has been concentrated on the change from 0.1 Hz to 1 Hz.

Group 1 illustrates the effect of a small intravenous dose of tubocurarine. In four of the ten volunteers there was no change either in the initial twitch height or after the change of frequency (i.e., no detectable change from control conditions): these volunteers made no complaint of dizziness or diplopia. In two cases there was no change in the twitch height at 0.1 Hz when tubocurarine was given but a change in frequency from 0.1 Hz to 1 Hz caused a diminution of the twitch height (figs. 1, 6). In the case of the other four volunteers there was diminution of the twitch height at 0.1 Hz after tubocurarine was given

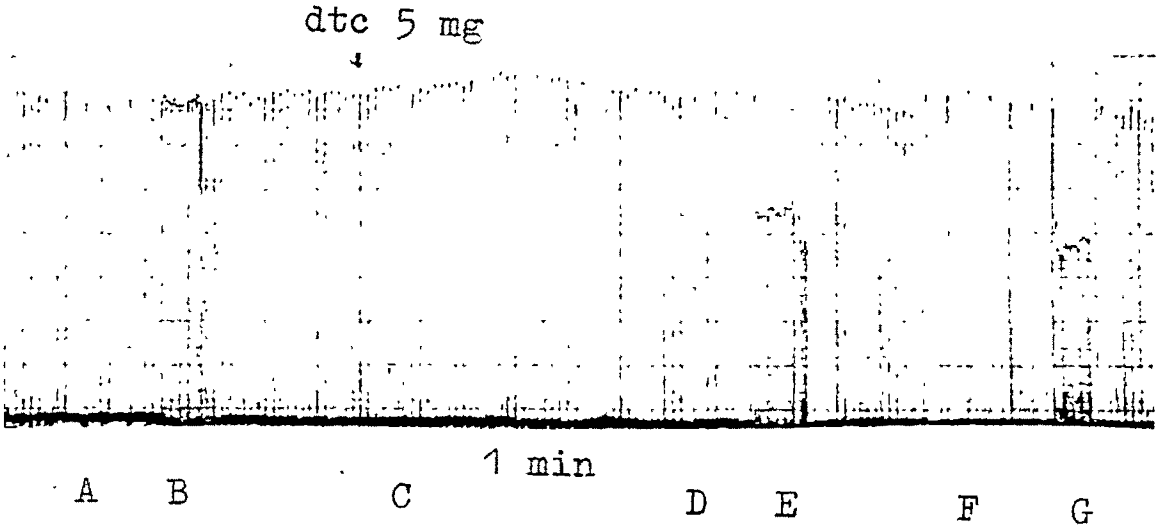

FIG. 6

The effect of tubocurarine on the twitch height in a volunteer. There was no change in twitch height when the frequency of stimulation was increased from 0.1 Hz to 1 Hz (A to B) before tubocurarine was administered. After tubocurarine 5 mg was administered, this change in frequency caused a diminution of twitch height (D to E and F to G). Note the slight increase in the height of the muscle twitch after tubocurarine was given.

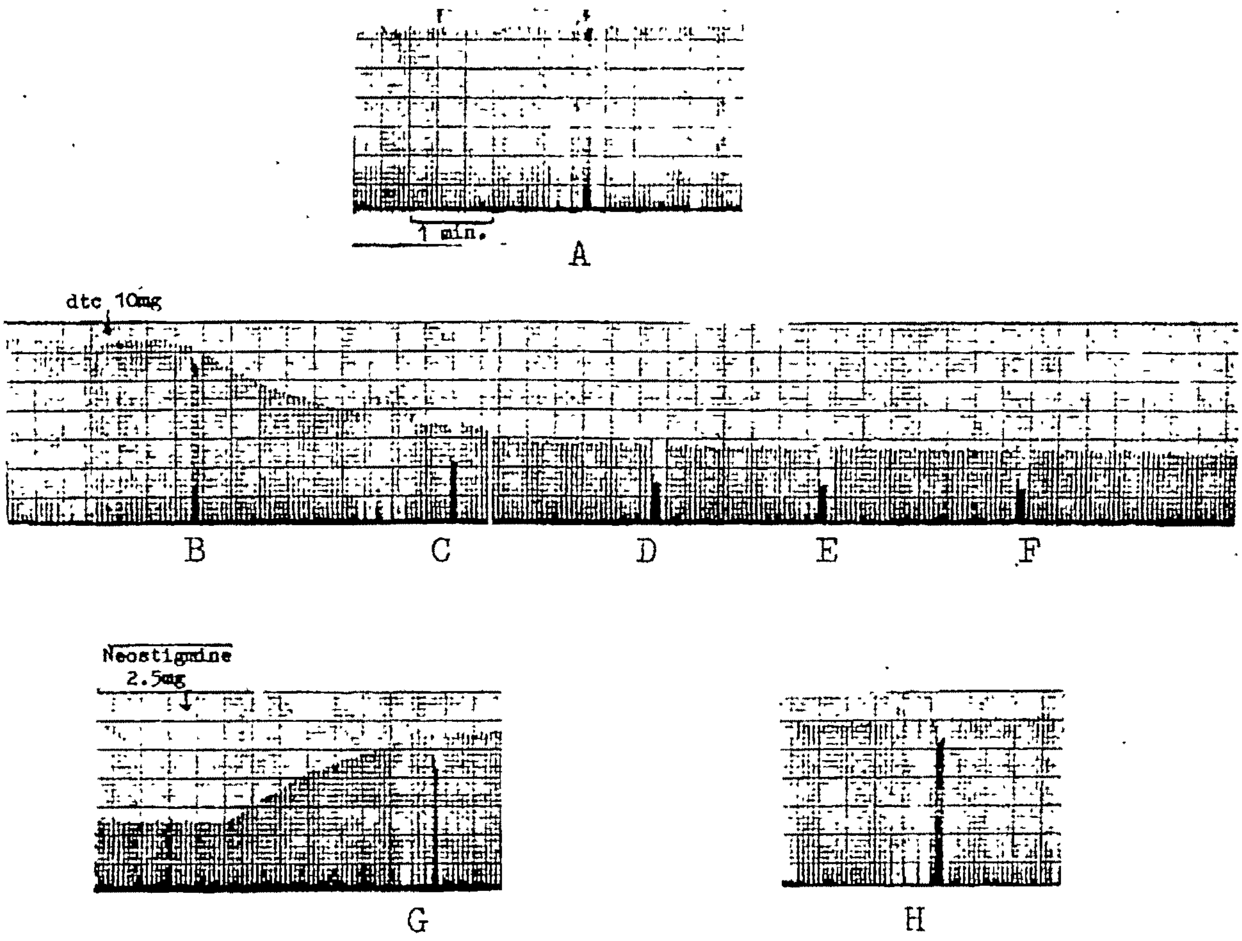

FIG. 7

The effect of tubocurarine on the twitch height in an anaesthetized patient. Change of frequency from 0.1 Hz to 1 Hz before tubocurarine was given caused no change in twitch height (A). Change in frequency from 0.3 Hz to 1 Hz during curarization caused diminution in twitch height (B, C, D, E, F). After neostigmine there is recovery of the twitch and with depression of the twitch height on the change of the frequency from 0.1 Hz to 1 Hz (G, H). Note that the per cent depression of the twitch response at 1 Hz is much less after neostigmine than before.

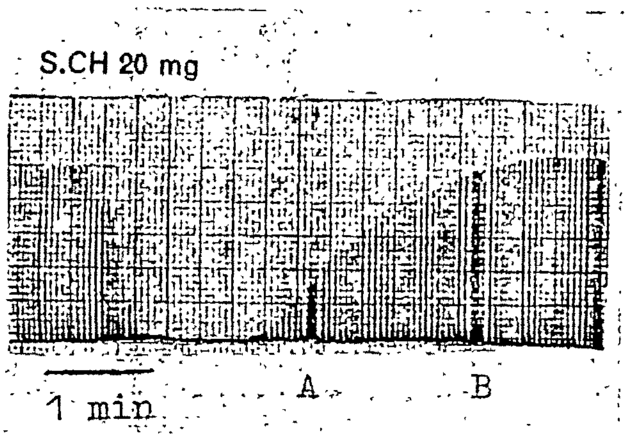

FIG. 8

A tracing illustrating the phenomenon shown diagrammatically in fig. 4: increasing the frequency of stimulation from 0.3 Hz to 1 Hz during recovery (A, B) did not change the slope of the recovery curve. (S.CH = suxamethonium.)

and a relatively more marked diminution when the frequency of stimulation was increased from 0.1 Hz to 1 Hz (fig. 2). All the volunteers who showed these changes had diplopia, slurred speech and found difficulty in opening the eyes.

The changes observed in the anaesthetized patients in group 2 were qualitatively the same as in group 1 but the quantitative changes were greater (fig. 7). In group 3 the large dose of tubocurarine administered usually resulted in complete ablation of the twitch, but during recovery, both before and after neostigmine, the same pattern of partial curarization seen in groups 1 and 2 was observed.

(b) *Train of four stimuli.*

In group 1 it was found that three of the volunteers showed no change in twitch height in response to the train of four stimuli (i.e., there was no change from control twitch heights) after the tubocurarine was administered. In five of the volunteers there was no change in the first twitch response of the train of four but diminution of the subsequent three twitches (fig. 3B) and in two volunteers there was depression of the first twitch response as well as diminution of the subsequent three twitches (fig. 3C, D). One of the volunteers who showed no diminution of twitch response to the changes of frequency studied showed some diminution in the second to fourth twitch height of the train of four. During recovery from tubocurarine each of the four twitch heights gradually returned to control levels; the first was the mos rapid to return and the fourth was the slowest.

The same pattern was seen in the anaesthetized patients in groups 2 and 3; and it was, of course found that the recovery process was accelerated by neostigmine (figs. 9, 11). When the larger doses of tubocurarine were given (i.e., in group 3), however, there was complete ablation of the twitch

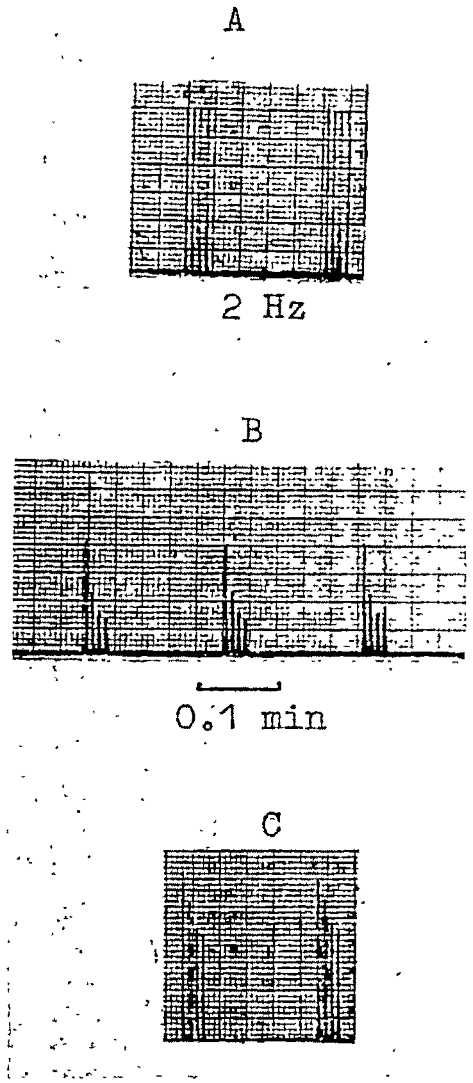

FIG. 9

The responses to the train of four stimuli. (A) Control tracing. (B) Obtained 5 min after tubocurarine 10 mg. 10 min after tracing B obtained, neostigmine 2.5 mg was administered; 4 min after this there was a substantial degree of recovery (C).

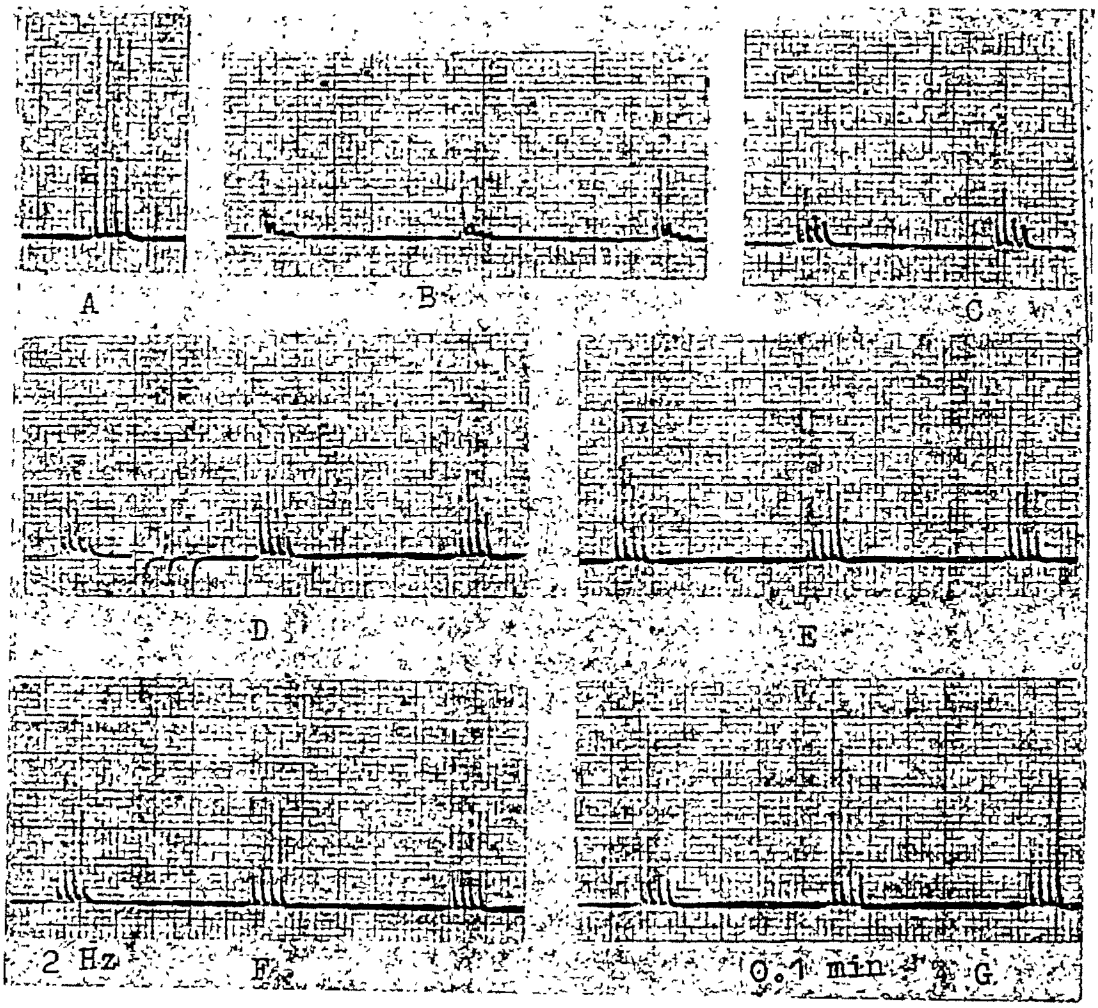

FIG. 10
The responses to the train of four stimuli. (A) control tracing. (B) shows the maximum depression of the response obtained after administration of tubocurarine 20 mg. (C, D, E, F, G) show spontaneous recovery at 10-min intervals.

which reappeared either during spontaneous recovery or when neostigmine was given (fig. 11).

Pattern after suxamethonium (group 4).

Suxamethonium usually abolished the twitch response completely. When recovery was taking place it was found that change of stimulus frequency from slower to faster rate did not result in a change in the slope of the recovery curve (figs. 4, 8). The response to the train of four stimuli was ablated by suxamethonium but on recovery all four twitch responses were of equal height when the twitch response reappeared if halothane was not being used in the anaesthetic (figs. 5B, 12A). In the case of prolonged halothane anaesthesia, however, small doses of suxamethonium led to some degree of "fade" in the responses to the train of four stimuli during both the onset of action and recovery from suxamethonium (figs. 5C, 12B, C).

DISCUSSION

Methods used clinically to assess the degree of neuromuscular block are mostly dependent on the pattern of evoked muscle response to change in stimulus frequency (Churchill-Davidson and Christie, 1959).

(a) *Observation of the twitch response to single repeated nerve stimuli.*

(As by the Block-Aid Monitor; Burroughs Wellcome Ltd.) This method will only detect considerable degrees of curarization, but it may be helpful in deciding whether prolonged apnoea after anaesthesia is peripheral or central in origin.

(b) *Failure to sustain tetanus (tetanic fade).*

The extent of this failure is dependent on the frequency and duration of stimulation (Gissen and Katz, 1969), and furthermore fade may be absent during a 40–50 per cent block following tubocurarine (Katz, 1965). Heisterkamp, Skovsted and Cohen (1969) showed that the mean twitch tension was reduced to 35 per cent of control values after tubocurarine (patients anaesthetized with methoxyflurane); 63 per cent of these patients failed to demonstrate fade when stimulated with a tetanic volley of frequency 30 Hz and duration 3 sec.

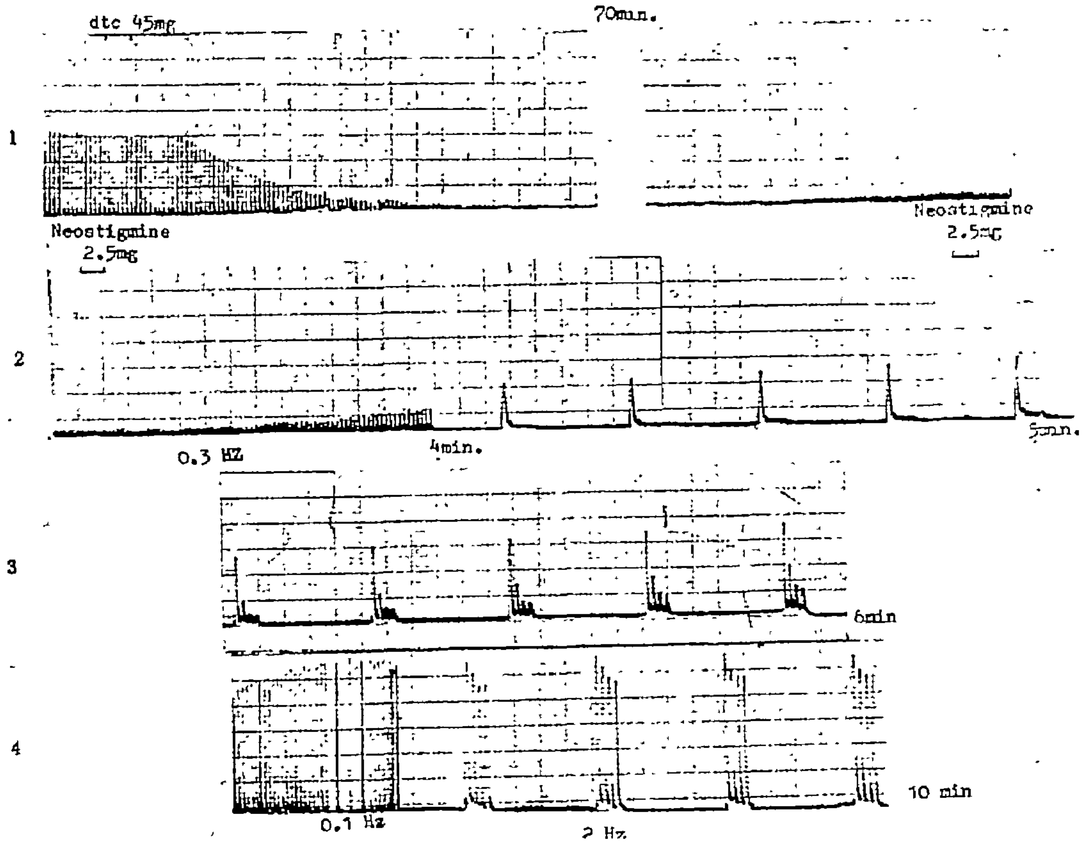

FIG. 11

A 50-year-old male patient, 68 kg. Anaesthesia was induced with thiopentone and followed by tubocurarine 45 mg (panel 1), and maintained on nitrous oxide/oxygen and IPPV. Complete ablation of the twitch response at 0.3 Hz was observed after 4 min. Spontaneous recovery of the twitch at the same frequency appeared 70 min later.

Panel 2. Neostigmine 2.5 mg was given 80 min after tubocurarine. Recovery of the twitch response to 0.3 Hz stimuli was monitored for 4 min, after which trains of four stimuli at 2 Hz being repeated every 10 sec; note the appearance of the first response only which progressively increased in amplitude with small subsequent responses to the train of four stimuli. At the end of panel 2 a further dose of neostigmine 2.5 mg was given.

Panel 3 shows the gradual and progressive increase in the four responses 1 minute after the second neostigmine dose.

Panel 4 shows an increase in the twitch height in response to stimuli at 0.3, 0.1 and 1 Hz respectively. Note that the twitch height is higher than the control before tubocurarine, yet there is still some fade in the four responses to the train of four stimuli 10 min after the first neostigmine dose.

(c) *Post-tetanic potentiation (PTP).*

This is markedly influenced by the duration and frequency of the preceding tetanus, as well as by the post-tetanic interval (Liley and North, 1953). PTP can occur in the absence of neuromuscular block (Von Euler and Brown, 1938; Botelho and Cander, 1953; Hughes and Morrell, 1957); in this case the phenomenon seems to be explained either by a change in the contractile response of the muscle or by repetitive firing of the nerve or muscle.

Gissen and Katz (1969) investigated the relationship between twitch, tetanus and PTP in an attempt to obtain an adequate index of neuromuscular block in man. They found that the response to tetanic stimulation at various frequencies gave a more sensitive index of neuromuscular block than did study of either twitch response or PTP: during partial neuromuscular block, tetanus is not maintained at higher frequencies of stimulation even though the magnitude of the twitch response to single stimuli may have returned to control level. As a result of their investigations these workers suggested that clinical nerve stimulators be modified to provide tetanic stimulation at several fixed frequencies (i.e., 25, 50, 100 and 200 Hz).

(d) *Monitoring the effects of anticholinesterase therapy on the twitch response.*

This may be a useful practical guide, but because these drugs have multiple actions, including that of post-junctional block (Roberts, 1963), the results cannot always be relied upon;

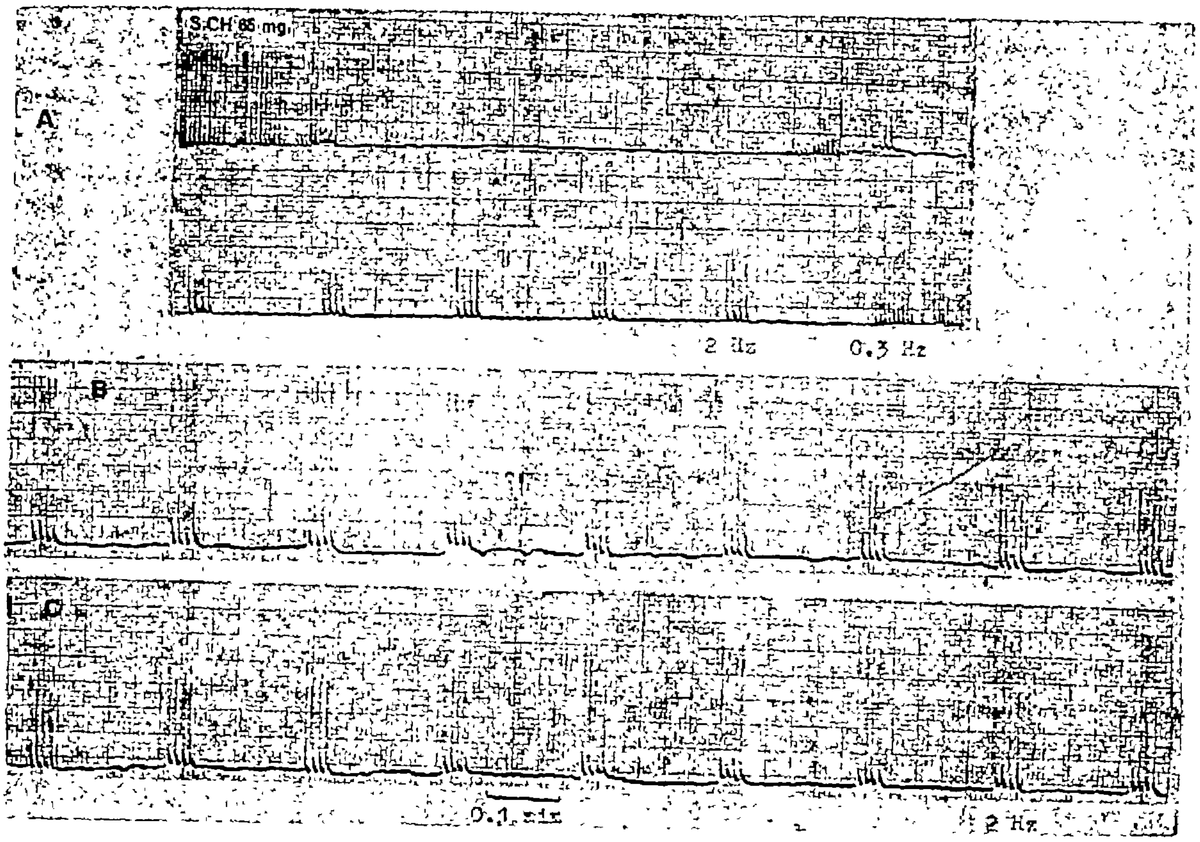

FIG. 12

Responses to the train of four stimuli at 2 Hz after initial responses to single stimuli at 0.3 Hz.

(A) Administration of and recovery from suxamethonium; anaesthesia with nitrous oxide and oxygen only.

(B, C) During administration and recovery from suxamethonium; anaesthesia with nitrous oxide, oxygen and halothane. Note the relative depression of the second, third and fourth heights. (S.CH = suxamethonium.)

and they offer neither proof of the presence of neuromuscular block nor a measurement of its degree.

(e) *Facilitation.*

This has been suggested by Berry (1966) as a possible method of assessing neuromuscular block in the absence of a control response before curarization. He utilized a facilitation phenomenon based on the application of two stimuli to the motor nerve with a very small time interval: this resulted in partial restoration of neuromuscular transmission in the curarized preparation—a phenomenon which he showed to be due to summation of endplate potentials. He compared the twitch tension resulting from a single stimulus and that resulting from a double stimulus with an interval of 1–1.8 msec between the two stimuli. Berry maintained that an increase in the muscle tension in response to the double stimulus may reveal evidence of neuromusular block and suggested that this might provide a technique which could be applied in the human subject to detect residual curarization.

Ideally the objective measurement of neuromuscular transmission should assess muscle strength as a proportion of fibres functioning at different twitch rates. It might be thought that comparison of isometric twitch heights obtained before a relaxant drug is given and again during recovery should provide a valid comparison, but there are several reasons why this is not so.

Unless monitoring is performed routinely, control levels of twitch tension are not available when postoperative muscle weakness is suspected; moreover complete stability of recording over a period of hours cannot be guaranteed. Drugs may cause repetitive nerve firing, as, for example, some of the anticholinesterases (Masland and Wigton, 1940; Blaber and Bowman, 1963) or repetitive muscle firing, as, for example, germine diacetate (Flacke, 1963). Repetitive nerve firing and repetitive muscle firing will both cause twitch heights out of proportion to the number of muscle fibres which are active, and this may result in twitch responses which are greater than normal despite the fact that a substantial number of endplates may remain blocked.

The methods of assessment of neuromuscular block investigated in this paper have several advantages over those in current use. Although they do not give a direct measurement of the proportion of fibres responding to motor nerve stimulation (this in any case will vary with the frequency of stimulation) it can be reasonably postulated that they afford a direct comparison between the degree of neuromuscular block in one patient and in another, and between the degrees of neuromuscular block found in the same patient at different times. These methods, moreover, do not require control levels of developed twitch tensions, which, in any case, can be misleading. They are simple and unlikely to be complicated by pure nerve or muscle effects, and do not cause the same amount of discomfort to the conscious patient recovering from anaesthesia as do tetanic rates of stimulation of 50 Hz or more.

The importance of particular levels of block as measured in this manner remains to be assessed. Tubocurarine 5 mg in conscious volunteers produced results which suggested a variable degree of block, though it might be added that the experimental findings using the two ratios appeared to correlate with the degree of diplopia and weakness as assessed clinically. A variation in response between individuals such as the result suggested could be due to a number of factors—for example, differences in dose/body weight ratio, in distribution, in plasma binding, and in muscle sensitivity.

While the degree of neuromuscular block demonstrated with tubocurarine 5 mg given to conscious volunteers is not associated with morbidity, the same degree of block might possibly be significant if it were present for long periods in a patient in the postoperative period. It is important, therefore, to establish the degree of reversal of neuromuscular block, which is compatible with safe return to the ward, and it seems probable that this can be achieved using the train of four stimuli (Ali, Utting and Gray, 1971). This test may also prove to be useful in assessing sensitivity to relaxants, and the likely dose requirements for particular operations. It could also be used as a tool for investigating the effects on neuromuscular transmission of other drugs and inhalation agents used during anaesthesia.

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FREQUENCE DES STIMULI DANS LA DETECTION DU BLOCK NEUROMUSCULAIRE CHEZ L'HOMME

SOMMAIRE

L'étude de la littérature au sujet de la physiologie de la transmission neuromusculaire a suggéré deux nouvelles méthodes pour évaluer le degré de bloquage neuromusculaire chez l'homme. Il y a en premier lieu une comparaison de l'intensité des tensions enregistrées de la convulsion, développée en réaction à des stimulations individuelles répétées appliquées à des fréquences différentes, et en second lieu l'estimation du degré de réduction de l'amputation des tensions de la convulsion, developpée en réaction à une courte série de quatre stimulations. Pour la première méthode, trois fréquences de stimulation ont été essayées (soit 0.1 Hz (CPS), 0.3 Hz et 1.0 Hz). On observa que l'augmentation de la fréquence de stimulation s'accompagna d'une réduction de l'amplitude de la réaction convulsive enregistrée chez les sujets curarisés, et que cette réduction sembla dépendre du degré de curarisation. Pour évaluer la seconde méthode, on utilisa une courte série de 4 stimulations à 2 Hz et on nota qu'il y eut une réduction progressive des réactions convulsives méchaniques successives, qu'on enregistra chez les sujets curarisés et que cette réduction sembla une nouvelle fois dépendre du degré de curarisation. Les auteurs croient que l'amplitude de la réaction convulsive à une fréquence plus élevée, exprimée en pourcentage de celle à un taux plus lent, ainsi que la dernière réaction de la série de quatre, exprimée en pourcentage de la première, peuvent servir utilement pour mesurer le degré de bloquage neuromusculaire chez l'homme.

REIZFREQUENZ ZUR ERMITTLUNG EINER NEUROMUSKULÄREN BLOCKADE BEIM MENSCHEN

ZUSAMMENFASSUNG

Das Studium der Literatur über die Physiologie der neuromuskulären Übertragung gab Anlaß, zwei neue Methoden zur Ermittlung des Grades eines neuromuskulären Blockade beim Menschen vorzuschlagen. Diese Methoden waren: (1) ein Vergleich der Höhe der bei Zuckung registrierten Spannungen, wie sie sich als Reaktion auf mit verschiedenen Frequenzen applizierte Einzelreize entwickelten: (2) eine Untersuchung des Ausmaßes der Amplitudenabnahme der bei Zuckung registrierten Spannungen, wie sie sich als Reaktion auf vier in kurzer Folge applizierte Reize entwickelte. Bei der ersten Methode wurden drei verschiedene Reizfrequenzen versucht (d.h. 0,1 Hz (CPS), 0,3 Hz und 1,0 Hz). Es wurde festgestellt, daß mit steigender Reizfrequenz die Amplitude der registrierten Zuckungsreaktion bei Personen unter Curare-Wirkung vermindert wurde und daß diese Reduzierung vom Grad der Curarisierung abhängig zu sein schien. Bei der zweiten Methode wurden vier in kurzer Folge applizierte Reize mit 2 Hz angewendet. Es zeigte sich, daß es bei Personen unter Curare-Wirkung zu einer fortschreitenden Abnahme der nacheinander registrierten mechanischen Zuckungsreaktion kam, was wiederum vom Grad der Curarisierung abhängig zu sein schien. Es wird angenommen, daß (zu 1) die Amplitude der Zuckungsreaktion auf die höhere Frequenz, ausgedrückt als Prozentsatz derjenigen bei der geringeren Frequenz und (zu 2) die letzte Reaktion auf die Folge von vier Reizen, ausgedrückt als Prozentsatz der Reaktion auf den ersten Reiz, möglicherweise nützlich sind, um den Grad einer neuromuskulären Blockade beim Menschen zu messen.

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ABSTRACTS

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(The name of the author presenting the paper is shown in bold type. *Indicates non-member.)

All authors have certified that, where appropriate, studies have been conducted with the approval of the relevant Human Ethics Committee or Animal Experimental Review Committee.

Diclofenac/dihydrocodeine or tramadol/tenoxicam after day-case gynaecological laparosopy?

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Analgesia following day-case laparoscopy still seems to be unsatisfactory. We have compared the standard combination take-home analgesia used in our unit with one using tramadol plus tenoxicam, as tramadol has been shown to be effective on its own after laparoscopy[1 2] and tenoxicam is effective for up to 24 hours.

Sixty ASA I–II day-case gynaecological laparoscopy patients were randomized to two groups and anaesthetized using propofol, tracrium, 0.5% isoflurane, fentanyl and droperidol 0.5 mg. Patients in the diclofenac/dihydrocodeine group were also given ketorolac 10 mg i.v., and on discharge, were given a take-home pain pack consisting of diclofenac 50 mg plus dihydrocodeine 30 mg to be taken as required six-hourly. The tenoxicam/tramadol group were given tenoxicam 20 mg i.v. during anaesthesia and on discharge were given a pain-pack consisting of tramadol 50 mg six-hourly as required with a mandatory tenoxicam on the first morning and an optional additional dose of tenoxicam 20 mg on the second morning.

Table 1 Postoperative pain, nausea and satisfaction scores

	Diclofenac/ dihydrocodeine (*n*=28)	Tenoxicam/ tramadol (*n*=27)
Pain, day 1, none/mild	21/28	21/27
Pain, day 3, none/mild	27/28	22/27
Nausea/vomiting	9/28	8/27
Unhappy with regimen	0/28	3/27

Both packs were appropriately arranged with placebo tablets so that a similar sequence of tablets was taken by both groups. This was to ensure that the study remained double-blind throughout. Metoclopramide 10 mg was also available to both groups to be taken for any nausea. If needed the first tablet of the pain pack could be taken after the operation before discharge. Four patients required morphine before discharge.

After discharge, all patients were telephoned at home on day 1 and 3, and assessed by semi-structured interview for pain score (none, mild, moderate, severe), activity, side-effects and tablet consumption. On day 3, an overall satisfaction score was given. Four patients were excluded from analysis because of failure of follow-up and one bcause of overnight admission (table 1).

There were no significant differences in pain scores, activity, side-effects or tablet consumption between the two groups. However there were three patients in the tenoxicam/tramadol group who experienced some dysphoria and preferred not to have that drug combination again. We conclude that our tenoxicam/tramadol regimen has no advantage over currently used medication following day-case laparoscopy.

Acknowledgment

We wish to thank Dr P. W. Duncan for facilitating Dr Erdmann's post from NHS funds.

Keywords: analgesics opioid, tramadol; surgery, day-case

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Cell wall fragments from Gram positive and Gram negative bacteria synergize to cause organ failure in the rat

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The incidence of septic shock resulting from Gram positive (G+ve) organisms has increased over the last 15 yr, and currently between 30 and 50% of sepsis is caused by Gram+ve bacteria.[1] Polymicrobial or mixed G+ve and Gram negative (G-ve) infections are associated with a particularly high mortality.[2] It has recently been shown in our laboratory that peptidoglycan (PepG) and lipoteichoic acid (cell wall fragments) from *S. aureus* act in synergy to cause shock and organ failure in the rat.[3] Here, we investigate whether very low-dose endotoxin (LPS) from *E. coli* can synergize with PepG from *S. aureus* to cause organ dysfunction in a rodent model of septic shock.

Male Wistar rats were anaesthetized with thiopental (120 mg kg^{-1} i.p.). At 15 min after surgery animals received either *E. coli* LPS (0.1 mg kg^{-1}, i.v., *n*=6), *S. aureus* PepG (3.0 mg kg^{-1}, i.v., *n*=6)

Table 2 Parameters of organ failure

Group	Creat (μmol $litre^{-1}$)	Bilirubin (μmol $litre^{-1}$)	AST (iu $litre^{-1}$)	ALT (iu $litre^{-1}$)	γGT (iu $litre^{-1}$)	Lipase (iu $litre^{-1}$)
SOP	24 (2)	2 (0.5)	214 (27)	85 (9)	1 (0.1)	7(3)
LPS (0.1 mg kg^{-1})	35 (3)	3 (0.3)	362 (3)	152 (21)	2.5 (0.3)	19(6)
PepG (3.0 mg kg^{-1})	29 (3)	1 (0.3)	277 (17)	108 (4)	2 (0.5)	14(4)
LPS+PepG	50 (6)*	6 (2.0)	553 (94)*	263 (55)*	4.2 (0.7)*	75(11)*

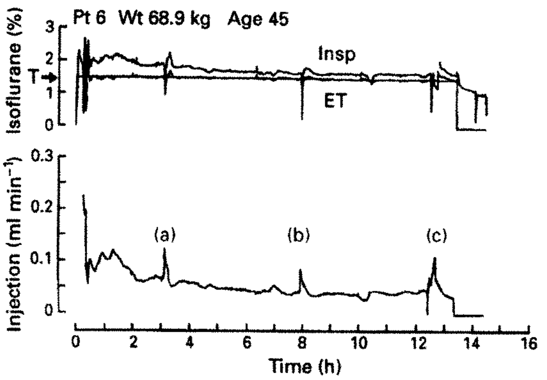

Figure 1 Inspired isoflurane and injection rate.

or a combination of LPS and PepG in the same doses given simultaneously (n=6). Another group of rats (sham-operated group (SOP), n=6) received an equal volume of the vehicle for LPS or PepG (saline). All rats received saline (6 ml kg^{-1} h^{-1}) during the experiment. Mean arterial pressure (MAP) and heart rate (HR) were monitored continuously and blood was taken for measurement of biochemical variables of organ injury at 6 h. Creatinine (Creat) for renal injury, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin and γ-glutamyl transferase (γGT) for liver injury and lipase for pancreatic injury.

Parameters of organ injury are given in table 2. Values are expressed as mean (SEM) *$P<0.01$ (ANOVA + Bonferoni's post-test).

These data show that cell wall fragments from G+ve and G-ve bacteria can synergize to cause organ injury in a rat model of septic shock. This may partly explain the increased mortality associated with polymicrobial and mixed infections, as well as the adverse effects of translocation of bacteria, or their cell wall components, from the gut lumen.

Keywords: infection, bacterial; complications, bacterial infection

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Uptake of isoflurane during prolonged anaesthesia

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We report on a study in progress into the uptake of isoflurane in humans. The opportunity arose to study this subject during the course of prolonged anaesthesia for major plastic surgery involving free-flaps. Uptake was measured by continuously recording the rate of injection of liquid isoflurane necessary to maintain a pre-set end-tidal concentration in a closed system. The rate of injection was Servo-controlled to maintain an end-tidal concentration of 1.3 MAC. Nitrous oxide was not used in the gas mixture. Bench tests were conducted to determine the gas-loss from our system and absorption into system components. We found that this did not exceed 5 μl of isoflurane per minute.

Figure 1 shows, in the top two curves, the inspired and end-tidal concentrations of isoflurane during a 14 h anaesthetic. The target end-tidal concentration is achieved after 20 min and closely maintained thereafter. The lower curve shows the rate of injection of isoflurane over the same period. At (a), (b) and (c) the soda lime was changed: also at (c) the syringe was recharged with isoflurane. The volume of isoflurane used for the entire procedure was 47 ml.

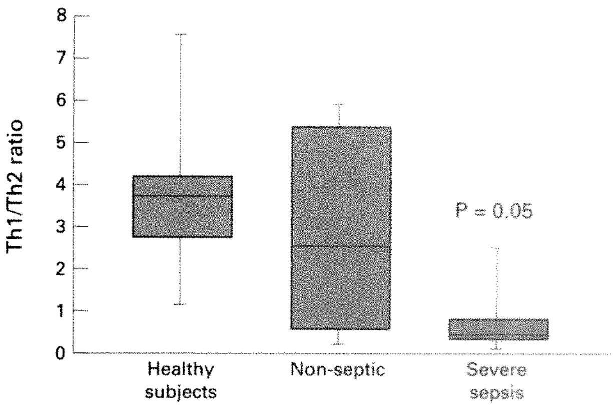

Figure 2 Th1/Th2 ratios in 10 healthy subjects, seven non-septic critically ill controls and nine patients with severe sepsis. Box and whisker plots show median, 25th and 75th percentiles and ranges as vertical bars.

It can be seen that uptake ceases to decrease after 6 h and shows little change for the remaining 11 h. This finding is not in accordance with computer predictions of anaesthetic uptake over long periods.

Keywords: anaesthetics volatile, isoflurane

Decreased Th1/Th2 cell ratios in patients with severe sepsis

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T-helper lymphocytes are important in both cell-mediated and humoral immunity. The particular type of immune responses is determined by the differentiation of precursor T-helper (Th0) cells into Th1 or Th2 cells. Each cell-subset secretes a particular array of cytokines which further augment the differentiation into that subset. Th1 cells produce interferon-γ (IFN-γ) and favour cell mediated immune responses, and Th2 cells secrete interleukin-4 (IL-4) and favour humoral immunity. The balance of cytokines produced in severe sepsis is likely to have a marked effect on Th-subset predominance and hence the nature of subsequent immune responses. We therefore measured Th1- and Th2-subsets in patients with sepsis syndrome compared with non-septic critically ill control patients.

Mononuclear leucocytes were isolated using density-gradient centrifugation, from nine patients with severe sepsis, seven APACHE-matched critically ill controls, and 10 healthy subjects. Cells were activated with ionomycin and phorbol ester in the presence of monensin, fixed, and stained with anti-CD3 and anti-CD4. After permeabilization with saponin, cells were then stained with anti-IFNγ or anti-IL-4 as appropriate, and quantified by flow cytometry. Data were assessed using the Mann–Whitney *U* test.

The median (range) Th1/Th2 ratio was 0.46 (0.2–2.5) in patients with sepsis, which was significantly lower than both non-septic controls; median 2.52 (0.2–5.9), (P=0.05), and healthy subjects; median 3.9 (1.2–10.8) (P=0.0003, fig. 2). These data suggest that in patients with sepsis Th2 antibody-mediated (humoral) immune responses predominate, leading to B cell proliferation, and preferential release of IL-4, IL-10 and IL-13. This type of response may lead to fibroblast activation and ultimately immunosuppression. Modulation of Th cell-subset predominance may present a novel therapeutic option in severe sepsis.

Acknowledgement

NRF is an Anaesthetic Research Society Vacation Scholar.

Keywords: immune response; infection; complications,sepsis

Time course of action of rocuronium during sevoflurane, isoflurane or i.v. anaesthesia

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Sevoflurane has previously been shown to potentiate the effects of other non-depolarizing neuromuscular blocking drugs,[1 2] but there are no reports of its action on rocuronium. In the present study we have compared the time-course of action of rocuronium during sevoflurane anaesthesia with isoflurane and i.v. anaesthesia.

Thirty adult patients aged 18–65 years and ASA I–II were included in the study with their written informed consent. They were anaesthetized with fentanyl 1–2 $\mu g\ kg^{-1}$ and propofol 1–3 mg kg^{-1}, 66% nitrous oxide in oxygen and either 1.5 × age adjusted MAC of sevoflurane (n = 10), or isoflurane (n = 10) or a propofol infusion (n = 10), according to a computer generated randomization. The ulnar nerve was stimulated at the wrist with supramaximal stimuli of 0.2 ms duration, in a TOF mode at 2 Hz every 12 s and the force of contraction of the adductor pollicis muscle recorded. Baseline neuromuscular responses were allowed to stabilize at the same time as the concentration of volatile agent was being stabilized over a period of 8–10 min. All patients then received rocuronium 0.6 mg kg^{-1} (approximately 2 × ED_{95}) and the times to onset and various end-points of spontaneously occurring recovery were recorded. These were times to recovery of T1 to 25%, 75% and 90% of control, and of the TOF ratio to 0.8, respectively. The data were subjected to ANOVA.

Table 3 Time (min) to onset and duration of block after rocuronium 0.6 mg kg^{-1} during sevoflurane, isoflurane and intravenous anaesthesia (mean (SD)); $^{*}P<0.05$ sevoflurane *vs* propofol and isoflurane

	Propofol	Sevoflurane	Isoflurane
Time to maximum block	1.02 (0.15)	0.96 (0.16)	0.90 (0.16)
Time to recovery of			
T1 to 25%	35 (9.2)	45 (13.1)	35 (6.1)
T1 to 90%	55 (19.4)	83 (29.3)*	56 (15.9)
TOF ratio of 0.8	62 (21.1)	103 (30.7)*	69 (20.4)
Recovery index	14 (6.9)	26 (11.7)*	12 (5.0)

Onset times were not significantly different for the three groups. The time to recovery to a T1 of 25%, although not clinically significant, was longer for the sevoflurane group (table 3). However the time taken for recovery to a T1 of 90% was prolonged for the sevoflurane group compared with the propofol and isoflurane groups (P= 0.0125). Similarly the time taken to recover to a TOF ratio of 0.8 was significantly prolonged in the sevoflurane group (P = 0.0017), as was the 25–75% recovery index (P = 0.0021). Our results show that the duration of rocuronium 0.6 mg kg^{-1} was significantly longer in patients anaesthetized with 1.5 MAC of sevoflurane compared with patients receiving 1.5 MAC of isoflurane or a propofol infusion.

Acknowledgement

Supported by DHSS (NI) and Abbott Laboratories.

Keywords: neuromuscular block, rocuronium; anaesthetics volatile, sevoflurane; anaesthetics volatile, isoflurane

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Effect of nitric oxide and superoxide on apoptosis in human neutrophils

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The use of inhaled nitric oxide therapy has become widespread in acute lung injury. Neutrophil apoptosis may also be important in regulating the inflammatory process by controlling neutrophil number and thus activity. We investigated the effects of nitric oxide and superoxide on apoptosis in lipopolysaccharide (LPS) neutrophils.

Neutrophils were incubated for up to 16 h with a pure nitric oxide donor (GEA-3162) and with a combined nitric oxide and superoxide (SIN-1) donor. Early apoptosis and late apoptosis and necrosis were assessed using annexin-V and propidium iodide staining respectively using a flow cytometric technique with and without LPS 1.0 $\mu g\ ml^{-1}$.

Annexin-V and propidium iodide staining increased over the 16 h-time period ($P\leq0.02$). Incubation in the presence of GEA-3162 in the absence of LPS significantly increased annexin-V staining at time-points 4 and 8 h (P=0.02), and propidium iodide staining at all time-points ($P\leq0.005$). SIN-1 increased annexin-V staining (P=0.04) and propidium iodide staining (P=0.04) in early culture but not at latter time-points in non-stimulated cells compared with blank. Increasing concentrations of GEA-3162 and SIN-1 caused an increase in annexin-V and propidium iodide at all time points ($P\leq0.005$).

These result suggest that increasing concentrations of nitric oxide could lead to an increase in apoptosis in lung neutrophils. This could have the effect of down-regulating neutrophil function in ALI and thus have a beneficial anti-inflammatory action. The availability of superoxide anion could determine the magnitude of this effect.

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Keywords: pharmacology, nitric oxide; blood, neutrophils

Psychological evaluation of intensive care unit survivors

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Few data describe the psychological and health outcomes from intensive care and most studies report short follow-up periods with disappointing response rates.

Table 4 Mean (SD) and sample sizes by age for Mini-Mental State (all patients), and SF-36 scores (patients with usable questionnaires at both 3 and 12 months)

Age (yr)	Live ICU discharges (n)	MMS	SF-36 at 3 months	SF-36 at 12 months	SF-36 Norms
Up to 45	50	21.9 (9.8) n=35	60.1 (20.5) n=24	65.0 (27.0) n=24	80.5
45–54	33	21.9 (9.9) n=31	58.0 (19.0) n=21	66.0 (20.7) n=21	78.9
55–64	48	23.5 (8.2) n=42	46.9 (24.2) n=31	51.1 (21.8) n=31	76
65–74	86	23.1 (7.3) n=77	55.8 (22.3) n=51	56.7 (25.9) n=51	NA
75 and over	71	21.7 (7.6) n=61	55.6 (21.0) n=21	46.8 (24.2) n=21	NA
Overall	288	22.5 (7.6) n=246	54.9 (22.0) n=148	56.8 (24.9) n=148	

We studied 369 consecutive patients aged over 6 yr who were discharged from the intensive care unit (ICU) over an 8-month period. Twenty-one patients had two admissions, two had three, only last admissions were analysed. Patients underwent a bedside evaluation within 48 h (Mini Mental State) and completed questionnaires at 3 and 12 months (SF36 Health Survey) (table 4).

Two hundred and eighty eight (78.0%) patients left the ICU alive of whom a further seven died before ward assessment. Of the 281 alive at ward assessment, 246 (87.5%) were assessed, nine (3.2%) were too ill or refused and 25 (8.9%) had been transferred elsewhere. One patient had no assessment for reasons unknown. Fifty-two more died before three months. Of the 229 presumed alive at 3 months, 194 (84.7%) completed the questionnaire, 10 (4.4%) refused or were too ill and 25 (10.9%) did not respond, some of these may have been dead. Twenty-three more died before 12 months. Of the 206 presumed alive at 12 months, 162 (78.6%) completed the questionnaire, eight (3.9%) refused or were too ill and 36 (17.5%) did not respond, some of these may have been dead. Four of the 162 questionnaires were too incomplete to score. One hundred and forty eight patients completed usable questionnaires at both 3 and 12 months (that is, some responded at 12 months but not at 3 months).

MMS scores were similar in all age groups. SF 36 scores were lower than normal values reported elsewhere. A one-way analysis of variance of improvement from 3 to 12 months, by age, shows significant differences ($P<0.01$), that is, strong evidence that improvement is related to age. Multiple comparisons confirm that younger patients (<65) improve ($P<0.05$) while older patients (>75) deteriorate($P<0.05$).

Acknowledgements

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Keywords: psychological responses, postoperative; intensive care

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Can isoflurane directly evoke inhibitory currents in neurones?

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Volatile anaesthetics have been suggested to directly gate chloride currents in hippocampal neurones[1] and cell lines.[2] It is known that barbiturates and steroids (at high concentrations) can directly gate a chloride current via the GABA$_A$ receptor–chloride channel complex.[3] We addressed the hypothesis that a directly gated inhibitory current contributes to isoflurane's pharmacological profile.

The patch-clamp technique was used to record whole cell currents from primary cultures of rat cortical neurones, in response to exogenously applied agents. The U-tube technique was used to apply fast (50–100 ms) pulses of GABA, pentobarbital (PB) and isoflurane, whilst bath perfusion (5 ml min^{-1}) provided background application of control saline, the competitive GABA$_A$ receptor antagonist bicuculline or the non-competitive chloride channel blocking GABA$_A$ receptor antagonist picrotoxinin. The concentration for maximal effect (*C*max), maximal current response (relative to GABA) and antagonist profiles for the three "agonists" were determined. Reversal potentials (V$_r$) were determined using gluconate and chloride-based pipette solutions.

Table 5 *C*max, maximal responses (as a percentage of the maximal reponse to GABA) and reversal potentials (mean (SD) (*n*))

Agent	*C*max (μmol litre^{-1})	Max response	V$_r$ K-gluconate	V$_r$ KCl
GABA	1000	100	−56.1 (3.3) (4)	−2.7 (0.5) (3)
PB	1000	20.9 (11.8)(15)	−55.1 (3.2) (9)	−3.5 (0.6) (3)
Isoflurane	3200	4.2 (2.6)(8)	−55.7 (5.0) (3)	−0.4 (7.3) (2)

Bicuculline (100 μmol litre^{-1}) reduced the maximal currents compared with their control values, GABA to mean 23% (SD) 9%, PB to 24% (18%) and isoflurane to 21% (11%). Picrotoxinin (10 μmol litre^{-1}) also reduced currents, GABA to 60% (10%), PB to 39% (24%) and isoflurane to 55% (5%) of control (table 5).

The extent of modulation by the antagonists in both ionic regimens, were not significantly different between the three groups ($P>0.05$ ANOVA). No "directly gated" isoflurane current was detectable at clinically relevant concentrations.

The reversal potentials and antagonist sensitivity suggest that all agents are acting via the GABA$_A$ receptor–chloride channel complex. A huge isoflurane concentration (equivalent to approximately 10 MAC) was required to elicit very small currents compared with GABA or pentobarbital. The current seen by us and Yang may simply result from potentiation of responses to synaptically released GABA from physiological systems, or reflect a small population of GABA$_A$ receptor subtypes with an isoflurane sensitive subunit composition.

Acknowledgment

We are grateful to the Association of Anaesthetists of Great Britain and Ireland for support.

Keywords: anaesthetics volatile, isoflurane; receptors, amino acid

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Thiopental decreases potassium evoked acetylcholine release from rat cerebrocortical slices

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Central cholinergic activity is involved in the control of consciousness.[1] We have recently shown that halothane decreases KCl evoked release of endogenous acetylcholine (ACh) from rat cerebrocortical slices with an IC$_{50}$ of 0.38% halothane.[2] In order to further explore the role of ACh in anaesthesia we have begun a major study of the effects of i.v. agents, and report here a study using thiopental.

Cerebrocortical slices (350 μm × 350 μm) were cut from Wistar rats. Slices were suspended in oxygenated (95% oxygen/ 5% carbon dioxide) Krebs buffer, pH 7.4 and incubated at 37°C for 40 min with choline 10 μmol litre^{-1} and 10 μCi of methyl-^{3}H-choline chloride. The slices were then aliquoted into two perfusion chambers and perfused at 1 ml per minute for 40 min with buffer containing atropine 0.3 μmol litre^{-1}, physotigmine 0.2 mmol litre^{-1} and hemicholinium-3 10 μmol litre^{-1}. Samples were then collected every 2 min. After three basal samples each chamber was exposed to KCl 40 mmol litre^{-1} for 2 min (S$_1$). After a further seven samples one chamber was exposed to either thiopental 200 or 50 μmol litre^{-1}. Perfusion was continued for a further 16 min before an S$_2$ pulse of KCl was applied. Released radioactivity was quantified using a scintillation spectrophotometer. The ^{3}H species was confirmed as ACh by high performance liquid chromatography. The S$_2$/S$_1$ ratio of released ^{3}H-acetylcholine was then calculated for control and drug-treated samples. The effect of thiopental on ACh release ratio was analysed by Wilcoxon rank-sum test and considered significant when $P<0.05$. All data are mean (SEM)

Potassium stimulation produced a monophasic Ca^{2+} dependent release of ^{3}H-acetylcholine during S$_1$and S$_2$, (fig. 3), yielding an S$_2$/S$_1$ ratio under control conditions of 0.59 (0.03) ($n=5$) thiopental 200 μmol litre^{-1} reduced the ratio to 0.39 (0.023) ($n=5$ $P=0.043$), representing mean reduction of 34.8% (2.8 %). Thiopental 50 μmol litre^{-1} produced no significant reduction in S$_2$/S$_1$ ratio.

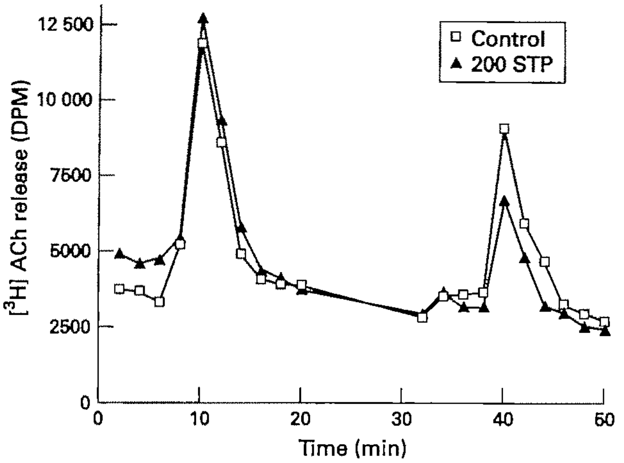

Figure 3 Thiopental (STP) 200 μmol litre^{-1} inhibits KCl evoked ACh release.

We have shown that thiopental decreases KCl-evoked acetylcholine release. This is further supporting evidence for the role of acetylcholine as an important neurotransmitter in the mechanism of anaesthesia.

Keywords: model, rat; anaesthetics i.v., thiopental; brain, cortex

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Haemolysis during cardiopulmonary bypass: do patients vary in susceptibility?

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Haemolysis occurs to some extent in all patients undergoing cardiac surgery. A raised free plasma haemoglobin concentration causes haemoglobinuria, and is associated with postoperative renal impairment.[1] Extrinsic factors relating to the bypass circuit have been implicated in haemolysis. This is thought to be the result of excessive mechanical shearing forces exerted on the red cell membrane.[2] The possibility that individual patients red cell membranes may vary in their susceptibility to mechanical forces has not previously been considered. Red cell osmotic fragility is a measure of membrane tensile strength in hypotonic solutions. It is an established test for gross membrane and cytoskeleton disruption.[3] This study tests the relationship between osmotic fragility and haemolysis in cardiac patients.

Twelve patients undergoing elective cardiac surgery were selected. Anaesthetic technique, cardiopulmonary bypass circuit, and blood flow on bypass were standardized. Aortic cannula size was chosen at operation on clinical grounds and could not be standardized. Arterial blood samples were taken before bypass, and at 15-min intervals thereafter. For osmotic fragility measurements, 50-μl samples of blood were incubated in 11 phosphate-buffered saline solutions of decreasing tonicity, and a 12th tube of pure water. Free haemoglobin in the supernatant was measured using absorption spectrophotometry at 540 nm and expressed as a percentage of that produced by pure water. During bypass free haemoglobin in plasma was assayed using the modified Drabkin's spectrophotometric method. Sigmoid curves of best fit for percentage haemolysis against sodium chloride concentration were drawn and osmotic fragility was compared from 50% haemolysis values using non-linear regression analysis. Patients were divided into two groups on the basis of haemolysis on bypass. Comparison between groups was by groups paired *t*-test.

Eight patients showed low/normal free plasma haemoglobin on bypass whilst four patients showed raised haemolysis with sustained haemoglobinuria. Osmotic fragility curves did vary slightly in individual patients throughout bypass, however the difference in 50% haemolysis values were not significant for the two groups ($P>0.05$).

The variation of haemolysis susceptibility from a limited sample of cardiac surgical patients does not appear to be associated with large differences in red cell osmotic fragility. Furthermore, the process of cardiopulmonary bypass itself does not appear to produce gross sub-lethal disruption of red cell membranes either as a result of mechanical trauma or oxidative damage. The most likely source of variability in haemolysis remains to be mechanical factors of flow/resistance relationships in the bypass circuit which cannot be controlled, however more sensitive tests of membrane tensile strength may be necessary.

Keywords: heart, cardiopulmonary bypass; surgery, cardiovascular; blood, haemolysis

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Collection of blood for cytokine research: a survey of anaesthetic/intensive care and immunology/pathology journals

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Many studies into cytokine biochemistry involve taking blood from humans or animals, either for assay of cytokine levels or for stimulation of cellular components under various conditions. These cellular components are known to be exquisitely sensitive to even the smallest amounts of endotoxin (lipopolysaccharide, LPS), for example, inconsistently in blood sample tubes, and any cytokine produced in direct response to the LPS may be falsely interpreted as being present in the circulation; in addition, exposure to traces of LPS may have significant effects on subsequent cytokine responses by "priming" the cells via surface receptors, even after only a few minutes' exposure in the sampling tube.[1-3] We surveyed articles involving research into cytokines, to study (i) whether researchers are describing efforts to minimize LPS contamination of blood sample tubes adequately; and (ii) whether there is any difference in practice between those publishing in immunology/ pathology (IP) journals and those publishing in anaesthesia/intensive care (AIC) journals.

All issues of the selected journals between January 1994 and December 1996 were searched by hand. IP journals were the *Journal of Immunology, Journal of Clinical Investigation* and *Journal of Clinical and Experimental Immunology*; AIC journals were *Anaesthesia, British Journal of Anaesthesia, Anaesthesia and Intensive Care, Canadian Journal of Anaesthesia, Anesthesia and Analgesia, Anesthesiology, Intensive Care Medicine* and *Critical Care Medicine*. The larger number of AIC journals reflected the fewer relevant articles per issue than the IP journals. Each paper involving the drawing of blood for cytokine assays and/or stimulation studies was studied for any mention of the steps taken to exclude LPS contamination during collection. Data were compared using Fisher's exact test, with $P < 0.05$ considered significant.

A total of 57 IP and 61 AIC papers were studied, with 3 (5.3%) and 8 (13.1%) respectively making any mention of proper precautions when collecting blood samples ($P = 0.2$).

Despite the problem of contamination of sampling tubes with LPS being well-publicized in the literature in the last 5–6 yr, and despite its crucial importance, we found that the vast majority of articles do not describe any efforts being made to avoid it. Whilst it is possible that researchers are taking appropriate steps and simply not describing them, we consider this to be unlikely given the very basic and vital importance of this component of scientific methodology and the emphasis placed on full description of methods in scientific articles. Much of the published cytokine literature must therefore be considered suspect until repeated with appropriate precautions and methodological descriptions.

Keywords: blood, cytokines; publications

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Effects of temperature and isoflurane on GABA$_A$ receptor function in cultured rat neurones: contribution to reduced anaesthetic requirement

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Hypothermia reduces the requirement for isoflurane anaesthesia such that at 20°C, in laboratory animals, no anaesthetic is required.[1] The GABA$_A$ receptor is a possible unifying molecular target for anaesthetic action.[2] This work assesses the sensitivity of GABAergic neurotransmission to temperature and to clinical levels of isoflurane to probe further the contributory role of fast synaptic inhibition in depressant effects on the CNS.

Synaptically coupled primary cultures of rat cortex were perfused with warm (37.2 ± 0.3 °C) or in separate cells cold (19.6 ± 0.9 °C) saline, n=8 each. Using the whole cell-patch clamp technique, spontaneous inhibitory postsynaptic currents (IPSCs) were sampled for 5-min periods before, during and after administration of 640 μmol litre^{-1} isoflurane (2 MAC equivalent). The time to half decay ($t_{1/2}$) and total charge transfer (area under the curve) were analysed by paired or unpaired t-tests as appropriate. Exogenous GABA was applied by U-tube to cells whose synaptic activity was silenced with tetrodotoxin 50 nmol litre^{-1}. Measures of GABA affinity and efficacy (EC$_{50}$ and the maximal response) were extracted from concentration response plots. Data are mean (SD) or for EC$_{50}$ values mean (95% confidence interval).

Control $t_{1/2}$ was prolonged by isoflurane at both temperatures. The $t_{1/2}$ was longer in cold than in warm cells. Total charge transfer was larger in the cold than in warm cells, but not altered by isoflurane. In previous exogenous agonist studies, isoflurane increased GABA$_A$ receptor affinity and decreased the maximal response.[3] In cold cells, the affinity of GABA and the maximal response to GABA are both significantly lower (P<0.05, unpaired t-test) than in warm cells (cold EC$_{50}$=13.0 (10.6–15.9) μmol litre^{-1}, max=39.3 (7.9), n=6; warm EC$_{50}$=8.6 (6.6–11.2) μmol litre^{-1}, max=56.9 (10.4), n=5)(table 6).

At the GABA$_A$ receptor chloride channel complex, the maximal current and affinity are lower in cold cells than warm, which we would expect to reduce the net inhibition. IPSC decay and charge transfer are, however, profoundly increased in cold cells. Isoflurane, like cooling, prolongs IPSC decay, but does not potentiate total charge transfer. There are similarities, but not absolute identity between the action of isoflurane and cooling on GABAergic function. These findings add support to the hypothesis that the GABA$_A$ receptor is a molecular target for isoflurane action, but suggest that this synapse is not the sole molecular target for thermal or pharmacological anaesthesia.

Acknowledgment

We are grateful to the Association of Anaesthetists of Great Britain and Ireland for support.

Keywords: hyperthemia; rat, model; anaesthetics volatile, isoflurane

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Mode of action of xenon assessed in cultured neurones from rat cortex

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The GABA$_A$ receptor has been proposed as a unifying target for anaesthesia.[1] Xenon is an effective anaesthetic but its mode of action is unknown. We have examined its cellular effects on two processes which are modulated by other inhalation agents: GABAergic inhibitory synaptic currents and passive release of neurotransmitter.[2]

A saturated solution of xenon was prepared by bubbling 100% xenon at 5 ml min^{-1} through normal saline. In n=7 cells with tetrodotoxin 50 nmol litre^{-1} to suppress evoked synaptic activity, miniature excitatory postsynaptic currents (mEPSCs) were sampled for 180-s periods in control saline, 120 s in saline containing xenon, then for 60 s again in control saline. A 100-s equilibration/washout time was allowed between sampling periods. The mEPSC frequency (Hz) was compared by paired t-test of control with xenon. Three of the cells had mIPSCs present that were not consistently overrun with mEPSCs, and these proved suitable for decay analysis. Their $t_{1/2}$ (time to half decay) was measured before, during and after xenon with the same sampling and equilibration periods as the mEPSC analysis.

After more than 2 h of xenon flow, when the temperature of the xenon saline was 24.1°C, presumably caused by evaporative cooling, the control saline and room temperature were both 25.8°C, it was noticed that bubbles were forming in the PTFE tubing downstream of the xenon saline reservoir, suggesting that slight warming to room temperature was causing pure xenon gas to "drop-out" of a saturated solution. Xenon produced no detecable effects on holding current at a V$_h$ of −40 mV in any of the cells tested. Xenon significantly reduced the mEPSC frequency from 17.9 (14.5) Hz to 13.3 (10.8) Hz (P<0.05). Frequency was depressed to 67 (20%) of control and recovered to 83 (36%). Interestingly, in the same cells, mIPSC $t_{1/2}$, a measure of postsynaptic GABA$_A$ receptor function was not affected.

The extracellular concentration of xenon during anaesthesia has not been reported: assuming delivery of a saturated solution at room temperature, we are exceeding clinical concentrations. Xenon has been shown to inhibit a Ca^{2+}-ATPase pump in synaptic plasma membranes,[3] this might be expected to increase intraterminal Ca^{2+} and increase transmitter release, in contrast with our findings. Xenon uniquely exerts a clear selective interaction with presynaptic processes (passive transmitter relase) compared with post-synaptic modulation of the GABA$_A$ receptor.

Acknowledgment

We are grateful to the Association of Anaesthetists of Great Britain and Ireland for support.

Keywords: model, rat; anaesthetic gases, xenon

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Table 6 IPSC decay ($t_{1/2}$) and total charge transfer (Area), with isoflurane at 37°C and 20°C

Temperature	Control	Isoflurane	*P* (ctrl *vs* iso)	*P* (warm *vs* cold ctrl)
Warm $t_{1/2}$ (ms)	6 (1.6)	11 (6.3)	0.0249	0.0000004
Cold $t_{1/2}$ (ms)	34 (8.9)	74 (20.1)	0.0007	—
Warm Area A.ms	4 749 (1924)	4 595 (2248)	0.918	0.01
Cold Area pA.ms	14 632 (8208)	12 595 (8043)	0.341	—

Effect of conduction block on basal immunoreactive-neuropeptide Y (ir-NPY) release in the spinal cord of the neuropathic rat

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In rats, ir-NPY is released spontaneously in the dorsal horn of the spinal cord, on the side ipsilateral to a chronic constriction injury of the sciatic nerve.[1] The likely site of origin is from primary afferent neurones,[2] although the stimulus resulting in release in not known. After nerve injury, primary afferent neurones behave abnormally, with the generation of spontaneous ectopic activity both at the nerve injury site and the dorsal root ganglia.[3, 4] If the spontaneous release of ir-NPY is caused by ectopic discharges, then blocking these impulses should abolish the new zone of spontaneously released ir-NPY found in the spinal cord of neuropathic rats.

In male Wistar rats, a chronic constriction injury was induced by placing four 4/0 chromic gut ligatures loosely around the sciatic nerve, under sodium pentobarbitone anaesthesia.[5] The International Association for the Study of Pain guidelines for the care of experimental animals were followed. After 10–14 days, levels of ir-NPY release were determined in rats (n=12) showing behavioural evidence of neuropathic pain. Under urethane anaesthesia, the lumbar spinal cord was exposed and microprobes coated with immobilized antibodies to NPY were inserted bilaterally into the spinal cord to a depth of 2.25 mm. Ir-NPY release was studied, first, under basal conditions, and then after conduction block with amethocaine gel proximal to the dorsal root ganglia. After removal from the spinal cord and incubation in ^{125}I-labelled NPY, the microprobe tip was placed on x-ray monoemulsion film, to give an autoradiographic image for each microprobe, that was then analysed. Binding of endogenous NPY results in deficits in binding of ^{125}I-labelled NPY, which was detected as a decrease in the optical density by a computerized image analysis system. Mean image analysis of defined groups of microprobes were compared, at 30 µs-intervals, and the differences between specified groups were assigned statistical significance using Student's unpaired t-test.

Spontaneous release of ir-NPY was confirmed on the side of the cord ipsilateral to the nerve injury.[6] This spontaneous ir-NPY release was not altered by conduction block proximal to the dorsal root ganglia, when studied for up to 3 h after conduction block. It is unlikely, therefore, that the spontaneous release of ir-NPY is caused by ectopic activity developing after nerve injury. Indeed, NPY may not be acting as a neurotransmitter at all, but is instead involved in the regenerative changes that occur in the dorsal horn after peripheral nerve injury.

Acknowledgements

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Keywords: model, rat; nerve, neurotransmission

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An observation on voluntary residual volume breaths

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Our understanding of the sensations of breathing and breathlessness is poor,[1 2] and largely drawn from studies of imposed loads in healthy subjects.[3] After breathing out to residual volume, I had the impression that I needed to breathe in to a higher volume on the next breath—that is, to a higher than normal end-inspiratory position. These are preliminary observations of that impression.

Breathing was recorded by respiratory inductance plethysmography, calibrated against a one-litre syringe; data were collected and analysed by microcomputer.[4] Subjects breathed quietly, sitting in a chair. When the breathing was regular, they were asked to breathe out in a residual volume manoeuvre, and then simply to continue breathing away as normal. The procedure was repeated seven times, the first two as practice, with at least 1 min between procedures. The breath preceding the residual volume breath was taken as baseline, and the measured variables (start-inspiratory position, end-inspiratory position, and tidal volume: all as ml) were measured against this breath for five breaths before and five breaths after the manoeuvre. Breaths from the five procedures were summed and averaged.

Measurements were made from four subjects, including myself. For three subjects, the end-inspiratory position was increased by about 100–300 ml after the residual volume manoeuvre, and this was their subjective impression (Findings from the fourth subject were unclear because she breathed in to a higher volume on the baseline breath, before the residual volume manoeuvre.) Start-inspiratory position also increased, so it was not just a matter of an increase in tidal volume for a few breaths after the manoeuvre. In all subjects, breathing pattern had settled back to baseline by the fifth breath.

This observation may be an artefact caused by stretching of the inductance bands. If it is real, it could be an effect of blood-gas changes induced by the respiratory volume manoeuvre, a response to stretch receptors in the chest wall or lung, secondary to the respiratory motorneurone output for the manoeuvre, or an effect of input from higher centres.

Keywords: ventilation, effects; lung, tidal volume; lung, mechanics

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Preoxygenation: sampling site and oxygen inflow rate

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Measurement of expired oxygen concentration (F_EO_2) at the face mask or within the oropharynx has been used to assess efficacy of preoxygenation (pre-O_2).[1 2] Our current practice during anaesthesia is to sample expired gases at a heat/moisture exchanger (HME) between the face mask and circle system. We aimed to study whether values of F_EO_2 at the HME during pre-O_2 are comparable with those at the oropharynx, and whether they are influenced by different oxygen flow rates in a circle anaesthetic system.

After Research Ethics Committee approval and written informed consent, 11 healthy adult female volunteers were recruited (age 29–36 yr, weight 57–67 kg). Each subject underwent four pre-O_2 cycles using a circle system, of 5 min each at oxygen inflow rates of 6, 8, 10, and 12 litre min^{-1}. An HME, standard face mask and nose-clip were used and volunteers breathed oxygen in the supine position. Between cycles, sufficient time was allowed for equilibration with room air; defined as when F_EO_2 reached 16–18%. During the pre-O_2 cycle, measurements of F_EO_2 were taken at 10-s intervals, up to 300 s (RGM Ohmeda). These measurements were simultaneously taken (a) at the HME and (b) in the oropharynx via a catheter mounted within a shortened Guedel airway.

Figure 4 shows a representative graph of median F_EO_2 during pre-O_2. At all oxygen flow rates studied, the initial values of expired oxygen were different at the HME (F_EO_2-HME) and the oropharynx (F_EO_2-OR) sites, values of F_EO_2-HME overestimating those of F_EO_2-OR. The times when the F_EO_2-OR and F_EO_2-HME

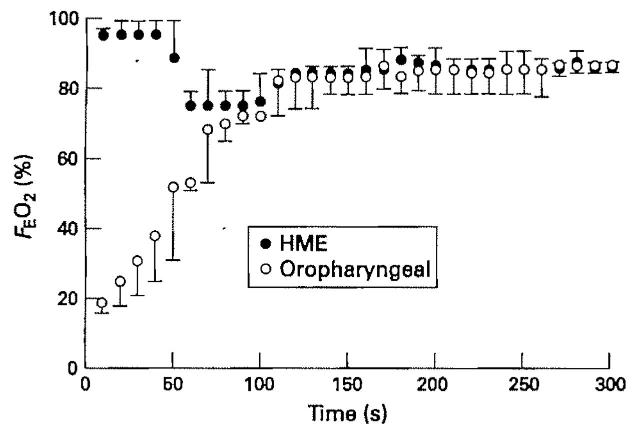

Figure 4 Median fractional expired oxygen concentration (F_EO_2) measured at the heat-moisture exchanger (HME) or oropharyngeal airway for an oxygen flow of 10 litre min^{-1}. Vertical bars denote interquartile range.

differences were small (< 5%) varied between 90 to 110 s. At this point, the median F_EO_2 attained for the various rates of oxygen inflow was: 70%, 73%, 78% and 83% at 6, 8, 10 and 12 litre min^{-1}, respectively. At the end of the pre-O_2 cycle, the median F_EO_2 attained with 6, 8, 10 and 12 litre min^{-1} oxygen was 80%, 85%, 87% and 87% respectively.

These results suggest that in healthy volunteers, monitoring F_EO_2 at the HME may be used to monitor pre-O_2 status, provided values of F_EO_2 are obtained after 110 s.

Keywords: anaesthetic techniques, preoxygenation; oxygen, measurement

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Predicting the response to adjustment of mechanical ventilation using a physiological simulator

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Adjustment of the ventilated patient's inspired oxygen fraction (FI_{O_2}) and ventilatory minute volume are performed in intensive therapy units (ITU) to attain adequate arterial gas partial pressures and plasma pH while reducing the hazards of mechanical ventilation. The Nottingham Physiology Simulator (NPS) may be used to predict the ventilated patient's physiological status and thus to predict the effect of the adjustment of ventilatory parameters. The aim of this study was to ascertain the usefulness of the NPS in predicting the ventilated patient's response to a change in ventilatory parameters.

The NPS is a computer simulation of original, iterative, cardiorespiratory and acid-base models. Thirty-one data sets were collected from 16 patients in the general ITU identified as requiring adjustment of mechanical ventilatory parameters. Each data set included temperature, haemoglobin concentration, tidal volume, respiratory rate, FI_{O_2} and arterial blood-gas analysis taken both before and 10 min after intervention. The simulation was aligned to the initial data set and was subsequently subjected to the same change in FI_{O_2} and minute volume as had been the patient. Correlation coefficients (*r*) were calculated between the predicted and observed change in Pa_{O_2}, Pa_{CO_2} and pH. 95% limits of agreement ($LA_{95\%}$) were calculated for the changes in these variables as bias ± 2.04 × SD of the difference between measured and predicted values.

All 31 data sets included manipulation of FI_{O_2}, while 14 also included adjustment of minute volume via change in tidal volume, respiratory rate or both. The mean absolute changes in FI_{O_2} and minute volume were 15.3% (SD 5.5%) and 16.6% (SD 10.3%), respectively. Correlation was strong and statistically significant ($P<0.01$) between predicted and measured changes in Pa_{O_2} ($r=0.99$), Pa_{CO_2} ($r=0.97$) and pH ($r=0.97$). The predicted absolute change in Pa_{CO_2} was consistently larger than the measured absolute change in Pa_{CO_2} (table 7).

The adjustments to minute volume and FI_{O_2} adequately represent those used in clinical practice. The limits of agreement between predicted and measured changes in the variables considered are acceptable for the use of the NPS to be considered as a clinical tool. The overestimation of the magnitude of change in Pa_{CO_2} may have been caused by an inadequate equilibration period between intervention and arterial gas sampling.[1] Additional errors may have been caused by coincidental alterations in patients' physiological profiles between intervention and arterial sampling

Keywords: ventilation, mechanical; model, simulation

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Table 7 Predicting the ventilated patient's response. Measured and predicted values are given as mean (SD). Regression equations relate values predicted by the simulator (S) to measured values (M)

	Measured	Predicted	Regression	$LA_{95\%}$
Pa_{O_2} change	5.76 (3.25) kPa	5.95 (3.51) kPa	S = 1.03M - 0.22	0.20 (0.20) kPa
Pa_{CO_2} change	0.60 (0.45) kPa	0.77 (0.55) kPa	S = 1.22M - 0.01	0.17 (0.06) kPa
pH change	0.04 (0.03)	0.04 (0.03)	S = 1.07M - 0.00	0.00 (0.004)

Fibreoptic intubation using the cuffed oropharyngeal airway and Aintree intubation catheter

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A ventilation/exchange bougie, the Aintree intubation catheter (AIC), has been evaluated for fibreoptic tracheal intubation via the laryngeal mask airway (LMA).[1] More recently a cuffed oropharyngeal airway (COPA) has been introduced which is based on the Guedel airway but has a pharyngeal cuff. As with the LMA, the internal dimensions of the COPA allow passage of the AIC mounted on a fibreoptic laryngoscope (FOL) so tracheal intubation is again feasible.

To evaluate the COPA in facilitating fibreoptic tracheal intubation with the AIC, 20 adult patients (scheduled for routine intermediate ENT surgery), ASA I–II, were recruited to a feasibility study. Patients at risk of reflux or in whom difficulty with intubation was anticipated were excluded. Anaesthesia was induced with propofol and alfentanil 15 µg kg^{-1}, and maintained with isoflurane in oxygen. Neuromuscular block was achieved with vecuronium 0.1 mg kg^{-1}. After 3 min, the COPA was inserted and manual ventilatory support continued. The AIC/FOL was introduced through an angle piece with a sealed port, and advanced through the COPA. The view of the larynx was graded as follows: 4, only cords seen; 3,cords plus posterior epiglottis; 2, cords plus anterior epiglottis; 1, cords not seen.[2] Ease of manual ventilation and any manipulations necessary were noted, and time from AIC/FOL insertion to intubation of the trachea was also recorded.

In 11 of 20 a view of the cords was possible at initial insertion (that is, grades 2–4). Lifting the jaw forward and/or tilting the proximal end of the COPA downward improved cord visualization to 19 of 20 In the remaining case, the FOL was easily guided below the epiglottis to then give a full view of the cords. Manual ventilation was satisfactory in all cases but only after increasing the fresh gas flow in 5 of 20. Time to intubation ranged from 70–139 s (mean 102 s). Intubation was straightforward in 17 of 20. In 2 of

20 additional manipulation of the FOL and COPA was needed to get below the epiglottis. Moderate difficulty occurred on one occasion when the AIC was not lubricated before insertion. Friction between it and the COPA made advancement difficult, altering the position of the COPA and causing intermittent loss of view of the larynx.

The COPA, like the Guedel airway on which it is based, is intuitive to use and facilitates good airway control. Unlike the LMA, its position in the oropharynx can be manipulated to improve the view with the FOL as necessary. Further work is planned to evaluate this method for difficult intubations.

Keywords: equipment, airway; equipment, tubes tracheal

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Ability of breathing system filters to prevent liquid contamination of breathing systems

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In 1994, a suspected incident of hepatitis C virus cross-infection occurred in New South Wales. It has been suggested this was caused by a patient coughing contaminated secretions into the breathing system which then acted as a reservoir for infection, as the breathing system was reused for subsequent patients.[1] Breathing system filters (BSFs) were not used for this surgical list. It has been suggested that some, but not all, BSFs available on the market would prevent liquid-borne contamination of the breathing system.[2] We therefore tested whether water penetrated through a range of filters under different conditions.

Twenty-nine different (5 pleated hydrophobic membrane and 24 electrostatic) BSFs with internal volumes ranging from 25 to 113 ml were assessed *in vitro* using a ventilator, breathing system and patient model. The BSF was orientated so that the filter membrane was either horizontal (with the patient side uppermost) or vertical. The flow and pressures in the patient model were measured for a total of 45 s during ventilation with a tidal volume of 0.5 litre and a frequency of 12 bpm. After 2 breaths, 5, 10 or 20 ml of water was injected onto the patient side of the filter. Breakthrough of the water to the breathing system side was assessed by visual inspection. The pressure decrease across the BSF was measured at a flow of 60 litre min^{-1} before and after the 45-s test period.

All the pleated hydrophobic membrane filters (H) and nine of the electrostatic filters (E) prevented the passage of water in all six tests (table 8). The pressure reduction increased in all the tests, which, in some cases, caused a reduction in the expiratory gas flow sufficient to cause an increase in PEEP and therefore the FRC of the patient model This was particularly marked with one of the pleated hydrophobic membrane filters. The increase in the resistance to gas flow of three BSFs, two electrostatic and one pleated hydrophobic membrane, was always less than twice the initial value. These three BSFs also prevented the passage of water. The incidence of the passage of water, and the increase in pressure reduction, was reduced with the filter element in a vertical orientation. Most manufacturers of BSFs contraindicate the use of a BSF with a patient with copious secretions However, if some BSFs are used with patients who do subsequently develop copious secretions, the penetration of liquid may make it necessary to replace the contaminated breathing system tubes after use.

Table 8 Results of water penetration tests

	Number of devices in which water breakthrough occurred						Number of devices in which the pressure drop more than doubled					
Vol	Filter orientation						Filter orientation					
added	Horizontol			Vertical			Horizontal			Vertical		
(ml)	E	H	Total	E	H	Total	E	H	Total	E	H	Total
5	3	0	3	0	0	0	5	1	6	4	0	4
10	9	0	9	4	0	4	11	1	12	7	1	8
20	14	0	14	9	0	9	22	4	26	16	1	17

Acknowledgment

This work resulted from the investigation of the performance of HMEs for the Medical Devices Agency.

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Keywords: complications, cross infection; equipment, filters

Comparison of the effects of mivacurium at the larynx, as assessed by video imaging, with the adductor pollicis

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Previous workers have shown that neuromuscular block at the larynx is more rapid in onset, of less intensity and faster recovery than that at the adductor pollicis.[1] We have demonstrated, using video imaging of the larynx and an accelerometer at the hand, that the onset of block is significantly faster at the adductor pollicis.[2] The aims of this study were to assess the onset, maximal intensity and recovery profile of mivacurium at the larynx and to compare this with both accelerometry and a force transducer at the hand.

Ten healthy patients (ASA I or II) were recruited. Anaesthesia was induced and maintained with propofol, and the lungs ventilated with 30% oxygen in nitrous oxide via a laryngeal mask airway (LMA). An accelerometer was attached to the left wrist and a force transducer to the right thumb. The vocal cords were seen using a fibreoptic endoscope The recurrent laryngeal nerve was stimulated as described previously.[3] A train-of-four stimulus was applied to all three sites every 15 s. Mivacurium 0.15 mg kg^{-1} was given after 3-min stabilization. The angle between the vocal cords was measured before and on maximal adduction for T1 of each stimulus. Results were analysed using one way analysis of variance and Student's paired *t*-test.

Data were analysed for eight patients comprising six men and two women aged 37 yr and weighing 81.1 (18.3) kg (mean (SD)) (table 9).

One way analysis of variance indicated a significant difference ($P<0.05$) between the three groups for each parameter. Paired *t*-tests indicated a significant difference between the larynx and the adductor pollicis ($P<0.05$) as measured by both force transducer and accelerometry but not between the two techniques at the hands.

Table 9 Comparison of adductor pollicis and larynx

	Adductor pollicis		
	Force transducer	Accelerometer	Larynx
Time to max block (SD) (min)	2.38 (1.38)	2.53 (0.75)	3.91 (1.46)
Maximal block intensity (SD) (% of T1)	0.65 (1.22)	0.06 (0.18)	15.88 (12.98)
Time to 75% recovery T1 (SD) (min)	23.34 (7.77)	22.08 (3.89)	13.97 (8.39)

Table 10 Leucocyte adhesion molecule mean channel fluorescence in group A (aprotinin) and group B (control). Data are mean (SD). *$P<0.05$, **$P<0.01$ within groups (Bonferroni). †$P<0.05$ between groups (t-test)

	CD18				CD11b	
	Monocyte		Granulocyte		Granulocyte	
	A	B	A	B	A	B
0	0.87 (0.22)	0.92 (0.23)	0.51 (0.10)	0.49 (0.10)	0.53 (0.14)	0.47 (0.11)
1	0.97 (0.27)	1.23 (0.40)	0.51 (0.12)	0.66* (0.25)	0.73 (0.20)	1.12 (0.52)
2	1.16 (0.31)	1.54* (0.61)	0.53† (0.14)	0.72**† (0.17)	0.74† (0.20)	1.45*† (0 52)
3	1.15 (0.23)	1.33 (0.54)	0.49† (0.08)	0.70**† (0.14)	0.72 (0.25)	1.35 (0 96)

We have demonstrated that following mivacurium 0.15 mg kg^{-1}, the block at the cords is slower in onset, less intense and faster to recover (to 75% baseline T1) compared with the adductor pollicis as assessed by accelerometry or a force transducer.

Acknowledgment

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Keywords: monitoring, neuromuscular function; measurement techniques, accelerometry; neuromuscular block, mivacurium

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Aprotinin inhibits leucocyte activation in an isolated cardiopulmonary bypass system

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The inflammatory response to cardiopulmonary bypass (CPB) comprises increased expression of the leucocyte adhesion molecules CD11b and CD18, shedding of the adhesion molecule L-selectin and an increase in the pro-inflammatory cytokine interleukin-8 (IL-8)[1] resulting in inflammatory cell adhesion to, and transmigration through, capillary endothelium. Aprotinin is a broad spectrum protease inhibitor used to prevent excessive blood loss at cardiac surgery. Recent evidence suggests that it may also have anti-inflammatory potential.[2] We examined the effect of aprotinin on the inflammatory response to CPB using an isolated CPB circuit.

Five healthy volunteers each donated 500 ml blood which was divided into equal portions (A) and (B). (A) was treated with 250 000 kallikrein inactivator units (KIU) of aprotinin (volume 25 ml) and added to a circuit primed with a further 250 000 KIU. (B) was treated with normal saline 25 ml and added to an aprotinin-free circuit. CPB was commenced and continued for 90 min. Flow, temperature, pH, P_{O_2} and P_{CO_2} were maintained within pre-set limits. Ten-ml blood samples were taken at donation (sample 0) and at 30-min intervals throughout CPB (1, 2, and 3). Expression of leucocyte adhesion molecules and HLA DR was measured by flow cytometry, and IL-8 production by an enzyme linked immunosorbent assay. Repeated measures one-way analysis of variance was used to test differences over time within groups. Differences between groups were analysed by t-tests

There was no significant difference between groups in terms of blood gas, packed cell volume or electrolyte values. Aprotinin inhibited the CPB-induced increase in monocyte and granulocyte CD18 ($P<0.05$and $P<0.01$ respectively) and the increase in granulocyte, but not monocyte CD11b ($P<0.05$). CPB had little effect on levels of L-selectin and HLA DR. The IL-8 rise was smaller in group (A) however the difference between groups was not statistically significant (table 10). These results suggest that high-dose aprotinin attenuates the inflammatory response to isolated CPB by inhibiting leucocyte activation.

Keywords: heart, cardiopulmonary bypass; blood, leucocytes

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Does the anaesthetic technique affect recovery of bowel function after radical prostatectomy?

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Recent work has focused on the the apparent ability of postoperative extradural analgesia with bupivacaine to provide more rapid return of bowel function compared with either extradural or i.v. morphine.[1] We designed this study to discover if the choice of intraoperative anaesthetic technique is an important factor in determining recovery of bowel function, intraoperative blood loss and incidence of deep venous thrombosis (DVT) in patients undergoing radical prostatectomy surgery.

Forty patients with adenocarcinoma of the prostate undergoing radical prostatectomy by a single surgeon were prospectively studied, using a randomized protocol. Group A (n=21) patients received general tracheal anaesthesia with thiopental/succinylcholine induction and maintainence with isoflurane/nitrous oxide/oxygen, i.v. morphine 20 mg and muscle block with pancuronium. Patients' lungs were mechanically ventilated. After the operation, these patients received i.v. PCA morphine until bowel sounds were present, and then oral ibuprofen 600 mg every 6 h and paracetamol plus hydrocodone 4 hourly on demand. Group B patients (n=19) received an intraoperative infusion of thoracic (T10/11) extradural bupivacaine 22.5 mg h^{-1}, followed by extradural morphine 4 mg at the end of surgery. "Light" general anaesthesia was induced with thiopental followed by spontaneous inhalation of isoflurane/nitrous oxide/oxygen via a laryngeal mask airway. The extradural catheter was removed when bowel sounds were present and patients were taking oral liquids. Further analgesia was then provided with oral ibuprofen and paracetamol/hydrocodone as above. Additional parenteral morphine was available to both groups if necessary. Ultrasonography was used to detect DVTs on postoperative day 2 or 3. Groups were compared using t-tests and chi-square tests as appropriate. $P<0.05$ was considered significant.

There were no significant differences between groups in anaesthetic or surgical time, time to first oral intake, or time to hospital discharge. Patients in Group B had earlier flatus (29.2 (11.1) h *vs* 39.4 (12.6) h) and earlier first bowel movements (36.0 (9.4) *vs* 48.2 (17.0) h). Group A patients had higher morphine requirements for the first 48 h after operation. There was a significant difference in intraoperative blood loss between Group A (1410 (811) ml) and Group B (936.4 (495) ml). No DVTs were detected in either group.

Although presence of a thoracic extradural block intraoperatively did facilitate return of postoperative bowel function, the difference between groups was not great enough to realize a difference in time to discharge from hospital in this study population. Perhaps the difference between groups would have been greater if an infusion of extradural bupivacaine had been continued postoperatively. A significant reduction in intraoperative blood loss was observed in the extradural group, probably because of lower arterial or venous pressures.[2]

Keywords: anaesthetic techniques, extradural; anaesthetic techniques, inhalation; surgery, urological

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Iontophoretically applied lidocaine reduces pain on propofol injection

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Iontophoresis is a method by which drugs can be transported through body tissues under the influence of an electrical current. Iontophoretic local anaesthetic has been shown to provide a greater depth of skin anaesthesia compared with EMLA cream and is effective in 10 min.[1] We have investigated the effect of iontophoretically-delivered lidocaine on the incidence and severity of pain on injection of propofol.

This was a double-blind study of 40 unpremedicated patients undergoing anaesthesia for day-case surgery who were allocated randomly to one of two groups. Patients in both groups had iontophoresis electrodes applied. The negative electrode, containing 1.5 ml of 4% lidocaine in a hydrogel was applied to the dorsum of the hand and the positive electrode to the dorsum of the wrist. The iontophoresis group received a current of 3.5 mA for 11.5 min applied across the electrodes and the sham group had the electrodes in place for the same time but with no current applied. Immediately after electrode removal, a 20-gauge i.v. cannula was inserted into the dorsum of the hand between the electrode sites. Pain on cannula insertion was assessed by a blinded investigator with a 10-cm visual analogue scale (VAS). Propofol 1% was then injected at a rate of 2 ml every 5 s and the patient asked to assess pain in the arm as nil, mild, moderate or severe at 10-s intervals for 30 s. Data were analysed by the Mann–Whitney *U* test.

There were no differences between the groups with respect to age and sex. Median (range) VAS on insertion of cannula was 1.1 (0–3.8) in the iontophoresis and 2.8 (0–8.6) in the sham group ($P<0.005$). Incidence and frequency of pain on propofol injection are shown in table 11. Pain was reduced significantly in the iontophoresis group at 10 ($P<0.002$), 20 ($P<0.001$) and 30 s ($P<0.001$).

We concluded that lidocaine delivered by iontophoresis reduces the incidence and severity of pain on propofol injection and that this effect is not simply the result of local application of lidocaine without electric current. We are at present comparing the technique with that of adding lidocaine to propofol.

Table 11 Incidence and frequency of pain on propofol injection

Group	Iontophoresis			Sham iontophoresis		
Time (sec)	10 *n* (%)	20 *n* (%)	30 *n* (%)	10 *n* (%)	20 *n* (%)	30 *n* (%)
No pain	20 (100)	15 (75)	15 (75)	12 (60)	4 (20)	5 (25)
Mild	0	5 (25)	5 (25)	3 (15)	8 (40)	5 (25)
Moderate	0	0	0	3 (15)	3 (15)	4 (20)
Severe	0	0	0	2 (10)	5 (25)	6 (30)

Keywords: anaesthetics local, lidocaine; anaesthetics i.v., propofol

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A non-isotopic technique for plasma volume measurement in the intensive care unit: comparison with a ^{125}I-albumin method

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The measurement of plasma volume and hence the calculation of circulating volume is rarely performed in the intensive care unit setting, although the information obtained might be of considerable value. This is probably because the standard measurement technique requires the use of a radio-labelled protein, which although accurate, requires access to a nuclear medicine department, and has all the difficulties associated with the use of radiation.

We have measured plasma volumes by a dilution technique using 20% albumin as marker, and compared the plasma volumes obtained using this technique with values obtained from the standard radio-labelled albumin method. Eleven patients in the intensive care unit, whose lungs were ventilated and who were receiving inotrope infusions, were given a known dose of ^{125}I albumin (5–10 mCi, depending on patient weight) and arterial blood samples were taken at 1 and 10 min for measurement of plasma activity and hence calculation of plasma volume. The patients then received 200 ml of 20% albumin (40 g) over 2 min, given via a central cannula. Arterial blood samples were taken before, then 1 min after the albumin bolus, and analysed for albumin concentrations using a bromocresol purple dye-binding assay. The plasma volume for each time-point was then calculated using the formula;

$$PVol0\ (\text{litres}) = \frac{bolus\ (g) - (0.2 \times Alb_1)}{Alb_1 - Alb_0} = \frac{40 - (0.2 \times Alb_1)}{Alb_1 - Alb_0}$$

The agreement between paired values of plasma volume obtained was compared using the statistical technique of Bland and Altman (fig. 5).

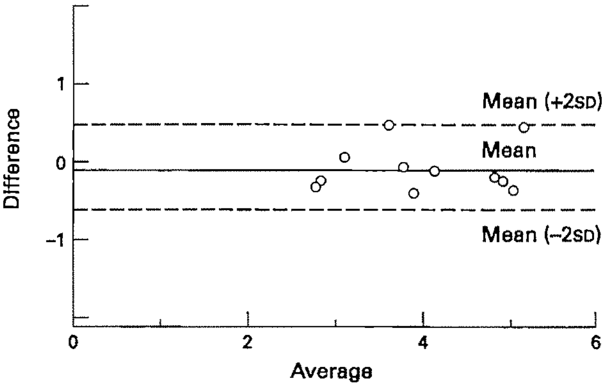

Figure 5 Bland and Altman plot.

The plasma volumes measured by the albumin dilution technique were smaller by a mean of 101 ml, with a standard deviation of 301 ml. The limits of agreement were −501 to +701 ml.

This simple bedside test allows rapid and moderately accurate estimation of the plasma and hence circulating volume.

Acknowledgement

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Keywords: protein, albumin; measurement techniques, plasma volume

Comparison of bench and fibreoptic jugular bulb oximetry during and after cardiac surgery

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Bench and fibreoptic methods of measuring the jugular venous bulb oxyhaemoglobin saturation compare favourably in patients with neurotrauma,[1] however, agreement between the two methods is less favourable during cardiopulmonary bypass (CPB)[2] and no comparison has been undertaken in the post-cardiac surgery period. The aim of this study was to compare the two methods both during and after cardiac surgery.

Table 12 Co-oximeter and fibreoptic measurements of blood samples

	Mean difference (Co-ox.%− Cath.%)	Limits of agreement	95% confidence interval of bias	Mean change in haemoglobin (g dl^{-1})
Intraoperative	−1.12	−20.29 to 18.05	−4.69 to 2.45	5.26
Postoperative	0.53	−6.39 to 7.45	−0.70 to 1.76	2.02
ANOVA	$P<0.001$			$P<0.05$

A fibreoptic venous oximetry catheter was inserted via the internal jugular vein and the tip placed in the jugular venous bulb, in 33 patients undergoing elective cardiac surgery The catheter was calibrated *in vivo*. Intraoperatively, multiple blood samples were taken and analysed using a bench co-oximeter. After the operation, the catheter was re-calibrated on the patients' arrival in the intensive care unit and further samples were analysed for up to 18 h. The co-oximeter and fibreoptic measurements were analysed using a method comparison analysis.[3] The level of significance was set at 5%.

Table 12 gives the results.

The range of differences between the two methods is greater intraoperatively than after the operation. Possible reasons for the lack of agreement intraoperatively are low blood flow during CPB allowing the catheter to abut the vessel wall leading to artefactual readings, and a greater change in haemoglobin concentration. After the operation there is a better comparison between the fibreoptic and bench co-oximetry readings.

Acknowledgement

This study was funded by SHERT-Grant Number 1424.

Keywords: surgery, cardiovascular; measurement techniques, oximeters

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Effects of controlled haemorrhage on the microcirculation during ketamine anaesthesia

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It has been shown in unanaesthetized rats that vessel diameter responses after a haemorrhagic insult may follow one of two patterns.[1] However the response of small (<30 μm) arteriolar dilatation appears to be detrimental to survival.[1] Previous studies from this laboratory using propofol[2] have shown that following haemorrhage of 10% blood volume the dilatory response is most prominent. The threshold at which this occurs is greater than a 20% decrease in mean arterial pressure (MAP). It is likely that the sympathomimetic action of ketamine may alter the threshold. This study aimed to investigate the possible beneficial effects of ketamine on the compensatory mechanisms in the microcirculation induced during haemorrhage and haemorrhage re-infusion.

Wistar rats (n=17, 120–200 g) were anaesthetized with a sleep dose of ketamine (60 mg kg^{-1}) via the tail vein and maintained with an i.v. infusion of ketamine (50–90 mg kg^{-1} h^{-1}). Animals were ventilated with 30% oxygen, cardiovascular variables were monitored and the cremaster muscle prepared for *in vivo* microscopy.[3] An equilibration period of 30 min was allowed before the study started. In all groups of animals (n=17) vessel diameters, flow and macromolecular leak were recorded every 10 min for 120 min. During haemorrhage (H, n=5) and haemorrhage re-infusion (HR, n=6) 10% of the blood volume was removed over 10 min (blood removed = 0.75 ml 100 g^{-1}). In the HR group, 30 min after blood removal, saline:blood (2:1) was re-infused over 10 min. At the end of the experiment sodium nitroprusside 10^{-3} mol litre^{-1} (SNP) was applied topically to the cremaster preparation and the vessels observed for a further 10 min to assess vessel responsiveness.

Immediately before haemorrhage arteriolar vessel diameters (μm) were as follows (mean (SEM)): A1 (104.8 (5.0)), A2 (48.6 (3.7)), A3 (20.4 (2.1)) and A4 (9.7 (0.9)). Initially, haemorrhage-induced hypotension, MAP decreased by 23.0 (3.7%) (mean (SEM), n=11). When MAP decreased by >45% (n=2) constriction of A1 arterioles was accompanied by dilatation of A3 and A4 arterioles. When MAP decreased by <28% (n=8) there was no change in A1 diameter accompanied by constriction of A3 and A4 diameters. No significant responses were observed in venules. Re-infusion returned the cardiovascular variables to pre-haemorrhage levels but diameters remained at the levels induced by haemorrhage for the remainder of the experiment. Compared with controls no significant macromolecular leak was observed following haemorrhage or re-infusion. There was no significant differences in blood-gases and pH between the groups of animals. SNP caused dilatation of all vessels and this was greatest in A3 and A4 arterioles, particularly in the H group.

Compared with our previous findings with propofol anaesthesia it appears that the frequency of the detrimental arteriolar dilatation in response to haemorrhage is reduced during ketamine anaesthesia.

Acknowledgment

This study was supported by a British Journal of Anaesthesia project grant.

Keywords: anaesthetics i.v., ketamine; complications, haemorrhage

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Little effect of ventilatory rate and tidal volume on end-expiratory pressure after cardiac surgery

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In 1994, one of us (RF) showed that significant end-expiratory alveolar pressures (EEP) could occur after cardiac surgery in Sweden.[1] In a second study,[2] done in Manchester, fewer patients developed clinically significant EEP (P=0.005, one-way analysis of variance), which was possibly explained by the use of larger tidal volumes and lower ventilatory rates in Manchester. (Different perfusion or ventilation techniques during cardiopulmonary bypass (CPB) might also have been important.) This study was designed to test the hypothesis that ventilatory rate and tidal volume affect the development of EEP in cardiac surgery.

Twenty-two patients undergoing cardiac surgery (16 male) were randomized to ventilation rates of either 10 or 20 bpm. The mean age was 61 yr (range 45–76). Anaesthesia was induced with fentanyl 1.7–2.5 mg followed by pancuronium. Ventilation was with 50% oxygen, 50% nitrogen with 0.5–1% enflurane. Tidal volume was adjusted to give an end-tidal $P\mathrm{co}_2$ of 3.5– 4 kPa. EEP was measured by pressing the "expiratory pause hold" button on the Servo 900C ventilator, set to give inspiratory and pause times 25 and 10% of cycle. This was done (a) before sternotomy and (b) after sternal closure. Flow and pressure were recorded on a Gould recorder from which expiratory resistance, compliance and time constants were calculated.

One patient (rate 20 bpm) became hypoxic after CPB, and this patient was withdrawn from the study. In the remaining 21, mean age, height, weight, BMI, and mean FEV$_1$ and VC as percentages of predicted did not differ between the two groups. There were no significant differences in EEP between the two groups before (P=0.07) or after surgery (P=0.2; Mann–Whitney U test) (table 13). Neither were there any differences in lung mechanics between groups. The differences in EEP between groups were thus a result as much to the shorter expiratory time, as to rate-related change in airway tone. However, women (n=6) had a large spread of values for end-expiratory resistance after surgery: 75 (0.5–188) cm H_2O litre^{-1}s^{-1} (median (range)) compared with men (n=15), 38 (0.5–69) cm H_2O litre^{-1}s^{-1}, (P=0.08; Tukey's HSD).

In animals,[3] rate and tidal volume have a small but significant effect on EEP. Choice of ventilator setting cannot explain the difference between the impressive EEP previously seen [1] and the modest values in the later paper.[2] Pooling the data from all three studies suggests that significant EEP is likely to be associated with increasing BMI and age.

Table 13 EEP (median and range) before and after surgery

	EEP (cm H_2O)	
Rate (min^{-1})	Before surgery	After surgery
10 (n=11)	0.5 (0.05–1.50)	1.0 (0.05–6.5)
20 (n=10)	1.0 (0.5–5.0)	3.0 (0.05–7.5)

Keywords: ventilation, airway pressure; ventilation, positive end-expiratory pressure

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Differential effects of volatile anaesthetics on myofilament calcium sensitivity in isolated ventricular myocytes

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In this study we have investigated the effects of halothane, isoflurane and sevoflurane on myofilament Ca^{2+} sensitivity in intact rat ventricular myocytes to determine its role in the negative inotropic effects of these agents.[1] Freshly isolated myocytes were loaded with Fura-2 AM to measure intracellular Ca^{2+} transients associated with contractions evoked electrically at 1Hz.[2] During each experiment, cells were superfused with physiological salt solutions containing (i) Ca^{2+} 1 mmol litre^{-1} (control), (ii) Ca^{2+} 0.5 mmol litre^{-1} and (iii) Ca^{2+} 1 mmol litre^{-1} plus halothane 0.3 mmol litre^{-1} or isoflurane 1 mmol litre^{-1} or sevoflurane 2.0 mmol litre^{-1}. Figure 6 shows Ca^{2+} transients and contractions at 1 and 0.5 mmol litre^{-1} Ca^{2+}. The decline in the contraction with Ca^{2+} 0.5 mmol litre^{-1} is a direct result of the smaller Ca^{2+} transient. One mmol litre^{-1} isoflurane decreased the Ca^{2+} transient to the same degree as 0.5 mmol litre^{-1} (fig. 6A) but the resulting contraction was smaller than that seen in Ca^{2+} 0.5 mmol litre^{-1}. This suggests that the sensitivity of the myofilaments to Ca^{2+} was reduced by isoflurane. Similar results were observed with halothane. In figure 6B however, Ca^{2+} 0.5 mmol litre^{-1} and sevoflurane 2 mmol litre^{-1} depressed both Ca^{2+} transients and contractions to the same degree. These results suggest that isoflurane and halothane depress, whereas sevoflurane has little or no effect on myofilament Ca^{2+} sensitivity. This would contribute to the greater sustained negative inotropic effect of halothane and isoflurane compared with sevoflurane.

Acknowlegment

This work was supported by a British Journal of Anaesthesia project grant.

Keywords: rat, model; anaesthetics volatile; ions, calcium

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Does propofol have a negative inotropic effect on isolated ventricular myocytes at clinically relevant concentrations?

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Although it is well known that propofol, an i.v. anaesthetic agent in widespread use, causes hypotension, it is controversial whether this is caused by direct myocardial depression, reduced systemic vascular resistance or a combination of both. We have tested to what extent propofol has a direct negative inotropic effect on isolated rat ventricular myocytes. Freshly isolated myocytes were bathed in a physiological salt solution containing Ca^{2+} 1 mmol litre^{-1} and stimulated electrically at 1 Hz. The decrease in cell length during contraction was measured optically. Propofol was applied via the bathing solution for 1 min. At concentrations of 5 μmol litre^{-1} and greater, propofol caused a sustained decrease in the amplitude of the contraction; the decrease was greater at higher concentrations. The decrease in contraction (as a percentage of the control contraction) is plotted against the propofol concentration (on a logarithmic scale). These data are fitted with a

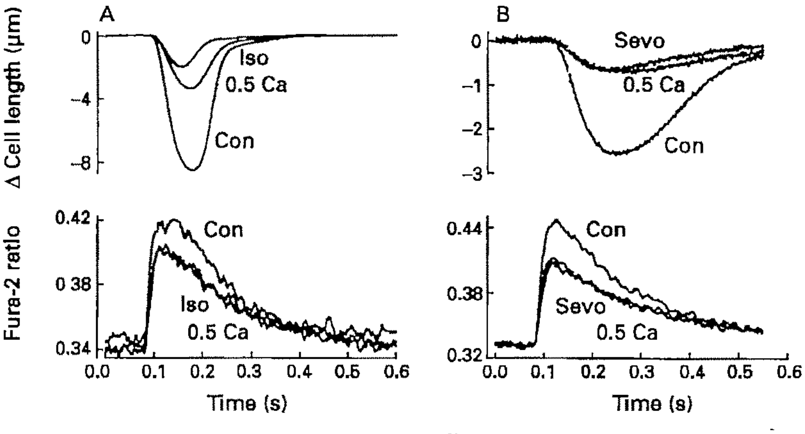

Figure 6 Change in cell length during contraction and corresponding Ca^{2+} transients on exposure to a solution (at 30°C) containing 1 mmol litre^{-1} Ca^{2+} (Con), 0.5 mmol litre^{-1} Ca^{2+} (0.5 Ca) and (A) 1 mmol litre^{-1} isoflurane (Iso) and (B) 2 mmol litre^{-1} sevoflurane (Sevo). Traces are an average of 15 sweeps recorded between 40 and 55 s after exposure to each solution.

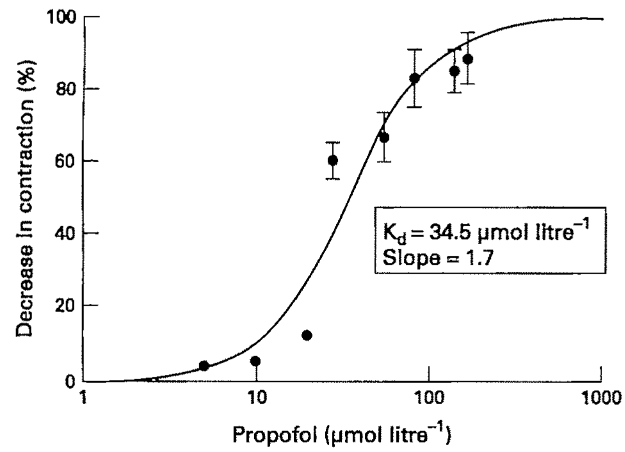

Figure 7 Percentage decrease in contraction caused by a 1 min application of propofol plotted against the propofol concentration. Data are presented as mean (SEM) of 3–13 cells. Experiments were carried out at 30°C.

standard dose-response curve. The Hill coefficient (a measure of the steepness of the curve) is 1.7 and the K_d (propofol concentration that decreases contraction by 50 %) is 34.5 μmol litre^{-1}. In patients, the anaesthetic K_d of unbound propofol is reported to be 0.4 μmol litre^{-1}.[1] Figure 7 shows that, at this concentration, propofol has no discernible effect on the contraction of rat ventricular myocytes. If these data are applicable to humans, they suggest that the hypotension caused by this agent is unlikely to be the result of a direct action on the heart. The mechanism underlying the negative inotropic effect of high concentrations of propofol is not known, but it could be the result of a decrease in the L-type Ca^{2+} current.[2]

Acknowledgement

Supported by a British Journal of Anaesthesia project grant

Keywords: anaesthetics i.v., propofol; heart, myocardial function

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Auditory-evoked response after co-induction of anaesthesia with midazolam and propofol

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A propofol-sparing action of midazolam has been demonstrated clinically.[1] Benzodiazepines and propofol are thought to act at differing sites in the GABA$_A$ receptor complex.[2] We have previously shown a correlation between the action of general anaesthetics and auditory-evoked response (AER) variables. AER waves Pa and Nb would reflect any major difference in the sites of action of midazolam and propofol, if co-induction of anaesthesia with these two agents was compared with propofol induction alone, to the same clinical end-point.

Forty unpremedicated patients, aged 18 to 55 yr, were randomized to receive midazolam 0.1 mg kg^{-1} (n=20) or saline in equivalent volume (n=20). After 3 min propofol was started by target controlled infusion (TCI) (Diprifusor) set at 8 μg ml^{-1} and paused intermittently. Loss of consciousness (LOC) was defined as both no response to verbal command and loss of eyelash reflex. Total propofol and TCI level at this point were recorded, and the TCI altered to continue at this level. The AER was recorded from electrodes at the vertex and inion. AER data (512–1024 consecutive sweeps, representing 80–160 s) were analysed for the awake period before starting midazolam or saline and the post-LOC period. Student's t-test was used to compare the log-transformed data from these two periods for the midazolam and saline groups.

After the start of propofol TCI, LOC occurred after a mean of 2.0 min in the saline group, compared with 1.5 min in the midazolam group. This difference was not statistically significant. However, there was a significant difference (P<0.001) between the two groups in the mean (95% CI) amount of propofol required to achieve LOC: saline group 2.4 (2.0, 2.7) mg kg^{-1} and midazolam group 1.3 (1.1, 1.6) mg kg^{-1}. Pa amplitude decreased and Nb latency increased (P<0.001) from the awake to the post-LOC period for all patients (table 14), but with no significant difference between groups.

These results confirm the propofol-sparing action of midazolam, and the AER data suggest that co-induction of anaesthesia using midazolam and propofol is achieved via a similar pharmacodynamic action of these two drugs.

Table 14 Geometric means (95% confidence intervals) for Pa amplitude and Nb latency

	Pa amplitude (μV)		Nb latency (ms)	
	Saline	Midazolam	Saline	Midazolam
Awake	0.71 (0.62–0.8)	0.61 (0.58–0.65)	43.5 (41.7–45.4)	43.8 (42.2–44.2)
Post-LOC	0.28 (0.23–0.37)	0.28 (0.26–0.31)	54.2 (50.3–58.2)	58.1 (53.6–62.9)
% change: awake to post-LOC	−60 (−69 to −47)	−54 (−66 to −35)	24 (13–37)	32 (21–46)

Keywords: hypnotics benzodiazepine, midazolam; anaesthetics i.v., propofol; monitoring, evoked potentials

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An open randomized comparison of alfentanil, remifentanil, and alfentanil followed by remifentanil in anaesthesia for craniotomy

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Remifentanil has been used in a range of major surgical procedures and appears pharmacodynamically similar to alfentanil. Recently, we have used computer modelling to simulate sequential infusions of alfentanil and remifentanil and predicted that this technique might offer rapid awakening at a lesser cost than using remifentanil alone.[1]

Forty-seven adults scheduled for elective craniotomy were randomly allocated to one of three opioid treatments. Alfentanil (ALF) 50 μg kg^{-1} then 50 μg kg^{-1} h^{-1} until dural closure. Sequential (ALF-REMI): alfentanil 50 μg kg^{-1} then 50 μg kg^{-1} h^{-1} until 2 h then remifentanil 0.25 μg kg^{-1} min^{-1}. Remifentanil (REMI) 1 μg kg^{-1} then 0.5 μg kg^{-1} min^{-1} reduced to 0.25 μg kg^{-1} min^{-1} after craniotomy. All groups received propofol at induction (0 5 mg kg^{-1} bolus + 10 mg every 10 s until anaesthetized) then 6 mg kg^{-1} h^{-1} until dural closure reducing by 1 mg kg^{-1} h^{-1} each 10 min to a minimum of 3 mg kg^{-1} h^{-1}. All were paralysed with atracurium and ventilated with 66% nitrous oxide in oxygen Propofol and remifentanil infusions were stopped at head bandaging.

For haemodynamic responses (MAP > 100 or HR >90), alfentanil 15 μg kg^{-1} or remifentanil 1 μg kg^{-1} and an infusion rate increase of 0.125 μg kg^{-1} min^{-1} were given. If present 2 min later this was repeated (and the alfentanil infusion rate increased by 15 μg kg^{-1} h^{-1} in ALF or ALF-REMI). If persistent, the propofol

Table 15 Data on anaesthesia, recovery and response

		ALF (n=18)	ALF-REMI (n=13)	REMI (n=15)
Anaesthesia (min)	median (range)	208 (101–337)	220 (137–689)	201 (121–558)
Extubation (min)	median (range)	16 (7–48)	17 (6–27)	13(9–21)
Obey command (min)	median (range)	17 (6–123)	22 (6–63)	13 (7–50)
Recovery room discharge (min)	median (range)	120 (86–225)	100 (45–181)	119 (58–158)
MAP>100 mm Hg or HR>90 min^{-1}	patients (episodes)	14 (30)	8 (29)	3 (8)
MAP<60 mm Hg	patients (episodes)	13 (26)	7 (18)	12 (12)
Analgesia in recovery	(patients)	9	6	10

infusion was increased by 2 mg kg^{-1} h^{-1}. For hypotensive episodes (MAP< 60) which did not respond to a fluid bolus the propofol infusion rate was reduced. Recovery room analgesia was given and recorded.

Anaesthesia, recovery and response data are summarized in table 15.

Two patients (1 REMI, 1 ALF) did not awaken after surgical complications and were excluded from recovery analysis. One patient (ALF-REMI) received intraoperative thiopentone and was excluded from all analysis. There were no significant between group differences for the times reported (Kruskall-Wallis test). Remifentanil infusion reduced haemodynamic responses but did not increase analgesia requirements in the recovery room. The sequential infusion of narcotics had no clinical advantages and involved additional work.

Keywords: surgery, neurological; analgesics opioid

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Oxygen and explicit semantic memory

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Moss and Scholey[1] gave volunteers air or 100% O_2 for 1 min before testing memory and reported a small improvement with O_2, from 5.4 to 6.4 out of 15 words presented. If correct their observation could affect anaesthetic practise and research. However, the difference might have been because of different capabilities of their groups. Therefore, we sought to reproduce this effect under similar experimental conditions, but with a more stringent study design.

Twenty healthy volunteers, randomized into two groups, participated in a twin double cross-over study. Group A breathed medical air from a non-rebreathing system for 1 min. One minute later a tape with a list of 20 words, standardized for concreteness and frequency, was played. Five minutes later, after a distracter task, volunteers wrote down the words they remembered. Fifteen minutes after air breathing, the same procedure was carried out with O_2 breathing. At least 48 h later, tests were repeated, however with exposure to O_2 first, and air second. Group B were similarly studied with all gas exposures in the inverse order. Volunteers were blinded as to which gas they were breathing. The written records were scored by a blinded observer. Words remembered in an incorrect grammatical form were scored as 0.5 (table 16).

Recall after air as the first gas of the day (A1 + B3) was compared with recall after O_2 as the first gas (B1 + A3); similarly, recall after air (B2 + A4) and O_2 (A2 + B4) as second exposures were compared. Finally, all exposures to air were compared with all exposures to O_2. None of the differences was statistically significant (P values 0.81, 0.09, and 0.28, Mann–Whitney test)

Table 16 Mean (range) number of words remembered out of a list of 20

	Day one		Day two	
	test 1	test 2	test 3	test 4
Group A	air: 9.9 (4–13)	O_2: 8.6 (5–13)	O_2: 10.8 (5–15)	air: 9.6 (3.5–15)
Group B	O_2: 7.6 (3–12)	air: 8.65 (4–13)	air: 9 (5–12)	O_2: 6.15 (2.5–9)

We were unable to demonstrate any enhancement of memory through O_2 administration.

The power of our study to exclude a substantial memory improvement (that is, an average of 3.5 more words remembered out of 20 presented) is 83%. However, a difference as small as one word can only be excluded with a power of 25–30 %, because of high intra- and inter- individual variability.

Keywords: memory; oxygen, therapy

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Effects of remifentanil and fentanyl on haemodynamic and auditory-evoked response changes after intubation

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Two clinical anaesthetic regimens, using either fentanyl or remifentanil (doses recommended by the pharmaceutical company) were compared, as part of a multicentre trial. Their efficacy in blocking the early cortical auditory evoked response (AER) and the cardiovascular response changes associated with intubation, were investigated.

Thirty-one patients (aged 18–65 years) were randomly allocated to one of two anaesthetic regimens. Group 1 received 1 µg kg^{-1} loading dose of remifentanil followed by an infusion of 0.5 µg kg^{-1} min^{-1}, propofol till loss of verbal contact, vecuronium 0.1 mg kg^{-1} then the lungs ventilated with oxygen, air and isoflurane to an end-expiratory concentration of 0.6%. Group 2 received a 3 µg kg^{-1} bolus of fentanyl before induction followed by the same anaesthetic regimen except that end-expiratory isoflurane was maintained at 0.8%. Heart rate and non-invasive arterial pressure were recorded 1 min before and 1 and 5 min after intubation. The AER was derived for 2.5 min before and after intubation. *Pa* amplitude was measured, $\log_{10}$ transformed and analysis of variance used to detect differences between the two groups.

After intubation there was a mean (95% confidence intervals) reduction in *Pa* amplitude of 12% (−32% to 14%) in the remifentanil group and a mean increase in the fentanyl group of 37% (−5% to 99%). The difference between remifentanil and fentanyl in the change with intubation was statistically significant (P=0.05). In both groups, significant increases in systolic and diastolic arterial pressure occurred 1 min after intubation and these increases were significantly greater in the fentanyl group compared with the remifentanil group (P=0.007, P=0.02 systolic and diastolic respectively) (fig. 8).

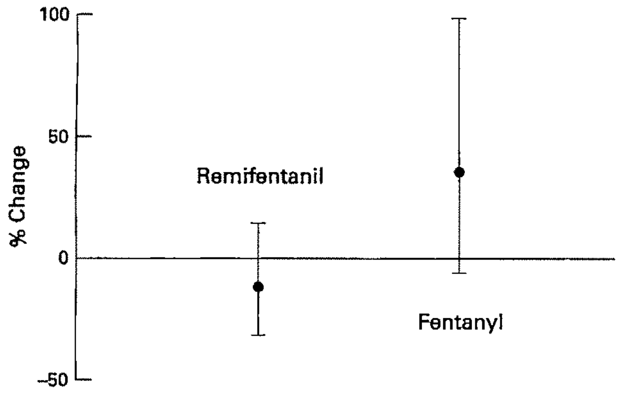

Figure 8 The mean % change (95% confidence intervals) in Pa amplitude after intubation.

This dose of remifentanil compares more favourably than fentanyl, at the doses recommended, in obtunding the stress response of intubation.

Acknowledgement

This project was supported in part by Glaxo-Wellcome

Keywords: monitoring, evoked potentials; analgesics opioid, remifentanil

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Sedation for neuroradiology revisited; comparison of three techniques for cerebral angiography

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Anaesthetist-administered sedation is still routinely used in our unit, despite improvements in radiology techniques and equipment, especially digital subtraction angiography. Previous work[1] showed that a propofol infusion with fentanyl gave earlier first recall compared with intermittently administered fentanyl and midazolam, but is this still true with current radiological techniques?

Patients ASA I–III, who were all orientated before cerebral angiogram, were randomized to be given anaesthetist-administered sedation by one of the three techniques used in our department. All patients were given a light oral lorazepam premedication (1–2 mg), or midazolam 1–2 mg i.v. several minutes before the start of the procedure. The first group were sedated with propofol 400 mg and alfentanil 2 mg in a 50-ml syringe delivered via a syringe pump, initially at 99 ml h^{-1} and then at 15–30 ml h^{-1} as indicated. The second group were given a propofol infusion (without alfentanil) as before but increments of fentanyl were given in addition. The third group were given increments of fentanyl and midazolam as indicated. All patients thus had a component of hypnosis, anxyolysis and analgesia. Both authors sedated similar numbers of patients.

All patients were sedated to a point where they lay calm and still, but usually maintaining one-way communication (obeying commands). All were given supplementary oxygen and routine monitoring was in place. We were particularly interested in time to orientation (date of birth, day of week), first memory after the procedure (table, department, ward, etc) and any recall during the procedure. Patients who could not be interviewed the next day, for example because they had gone for early surgery, were excluded from analysis. Several patients were excluded as they rebled after the angiogram (table 17).

We were surprised at the minimal differences between the techniques, compared with the differences in our previous study.[1] This may be partly because of the overall shorter length of the procedure (typically 10 min less), because of the benefits of digital subtraction angiography. It is also probable that the level to which we sedated our patients has changed in the intervening years and we would suggest that the success of a sedation technique depends more on the skill and experience of the administrator, rather than the actual technique used.

Table 17 Orientation, first awareness and incidence of intra-angiogram recall. No significant differences, ANOVA or chi-square as appropriate

	Prop/Alfent infusion	Prop Inf/ Fent Inc	Fent Inc/ Midaz Inc
Number	29	29	30
Duration (min, range)	35 (16–65)	38 (15–88)	35 (18–64)
Time to orientation (range)	3.7 (0–14)	4.3 (0–12)	5.1 (0–20)
First memory in Dept	22/29	16/29	20/30
Any recall during Angio	4/29	9/29	5/30

Acknowledgment

We are grateful to Dr P. W. Duncan for facilitating Dr Bewlay's post from NHS funds.

Keywords: sedation; measurement techniques, angiography

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Effects of sevoflurane with and without nitrous oxide on cerebral autoregulation as assessed by the transient hyperaemic response test

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Blood flow velocity (FV) in the middle cerebral artery (MCA), during a 10-s ipsilateral common carotid artery (CCA) compression (the transient hyperaemic response or THR test), can be used to quantitatively assess cerebral autoregulation.[1,2] Sevoflurane is a relatively new volatile agent. We aimed to assess its effects when used alone or with nitrous oxide (N_2O) on cerebral autoregulation using the THR test.

Eight patients (ASA I or II) aged between 18 and 40 yr presenting for routine non-neurosurgical procedures were studied. Baseline end-tidal (ET) carbon dioxide ($F_E'CO_2$) was measured and THR tests performed. Anaesthesia was induced using a standard technique. After tracheal intubation, the lungs were ventilated to maintain baseline $F_E'CO_2$. During the study, mean arterial pressure (MAP) was maintained to within +/- 10% of baseline using a phenylephrine infusion. THR tests were repeated at ET sevoflurane 2.2% in oxygen (sev1), 3.4% in oxygen (sev2), 3.4% with 50% ET N_2O in oxygen (sev1n) and 2.2% with 50% ET N_2O in oxygen (sev2n) in that order. Five minutes were allowed for equilibration after ET concentrations had been achieved. Strength of autoregulation (SA) was calculated as (F3 × P2)/(MAP × F1). F1, F2 and F3 were MCA FVs immediately before and immediately after application, and immediately after release of CCA compression, respectively. P2 (the estimated MAP in the MCA immediately after compression) was calculated as the greater of either MAP × F2/F1 or 60 mm Hg (assumed lower limit of autoregulation).[1]

The results are summarized in table 18.

Sevoflurane does not affect MCA FV or SA when used at 2.2% or 3.4% end-tidal concentrations in oxygen. Addition of nitrous oxide to the 2.2% but not the 3.4% group increases MCA BFV and impairs SA significantly, but this is a small study.

Acknowledgements

This study received funding from the Association of Anaesthetists of Great Britain and Ireland grant for the purchase of the Sci Med QVL120 transcranial Doppler ultrasonograph.
We would like to thank Abbott Laboratories Ltd for providing the sevoflurane for this study.

Keywords: monitoring, cerebral autoregulation, measurement techniques, transcranial Doppler; anaesthetics volatile, sevoflurane; anaesthetic gases, nitrous oxide

Table 18

	FI values (cm s^{-1})					SA (strength of autoregulation)				
	baseline	sev1	sev2	sev2n	sev1n	baseline	sev1	sev2	sev2n	sev1n
Mean	67.45	61.59	62.06	61.86	80.79†	0.96	0.93	0.88	0.90	0.79*
SD	8.81	11.83	16.05	15.46	16.59	0.11	0.06	0.08	0.09	0.12
ANOVA	P=0.045					P=0.016				
	t-test from baseline: P=0.019†					t-test from baseline: P=0.005*				

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POSTER PRESENTATIONS

Does abdominal muscle block contribute to occlusion pressure during anaesthesia?

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The decrease in airway pressure during occlusion of the airway at the start of an inspiratory attempt has been used as an indicator of inspiratory muscle force, to provide an estimate of inspiratory muscle force and an index of central respiratory drive. Using this index, respiratory depression associated with general anaesthesia has been attributed to changes in the impedance of the respiratory system.[1] As some respiratory activity occurs in expiratory muscles during anaesthesia, particularly when opioids are present, we investigated the relationship between expiratory muscle action and occlusion pressure.

We studied six healthy subjects after superficial surgery. The trachea had been intubated, and anaesthesia was with nitrous oxide, isoflurane, and an infusion of fentanyl. A catheter with two transducers (Gaeltec) was placed via the mouth to measure oesophageal and gastric pressure. Chest wall dimension changes during a control breath were measured with an optical system that allowed volume to be calculated directly. Airway pressure was measured at the mouth, during occlusion of the inspiratory limb of the breathing system, for an entire respiratory cycle. Data were recorded after digital conversion and analysed by spreadsheet (Excel). Changes in gastric pressure were noted during expiration in the breath preceding airway occlusion, and in airway, gastric, and oesophageal pressures during the first 0.3 s of the inspiratory attempt. Transdiaphragmatic pressure was calculated as Pga-Poes.

Between 15 to 20 breaths were studied in the following conditions: opioid infusion, with and without carbon dioxide stimulus, and then after opioid reversal with naloxone 0.4 mg, with and without carbon dioxide. The data (fig. 9) show a close relationship between gastric pressure changes during expiration and those at the onset of inspiration, but no clear evidence that abdominal relaxation contributes to airway occlusion pressure.

Keywords: ventilation, effects; muscle respiratory

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Pain control in day surgery: tramadol *vs* standard analgesia

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Successful pain management in day-care surgery demands efficacy without the adverse sequelae, which might delay or prevent discharge home. Tramadol has not been widely used intra-operatively or extensively investigated in day surgery, but has

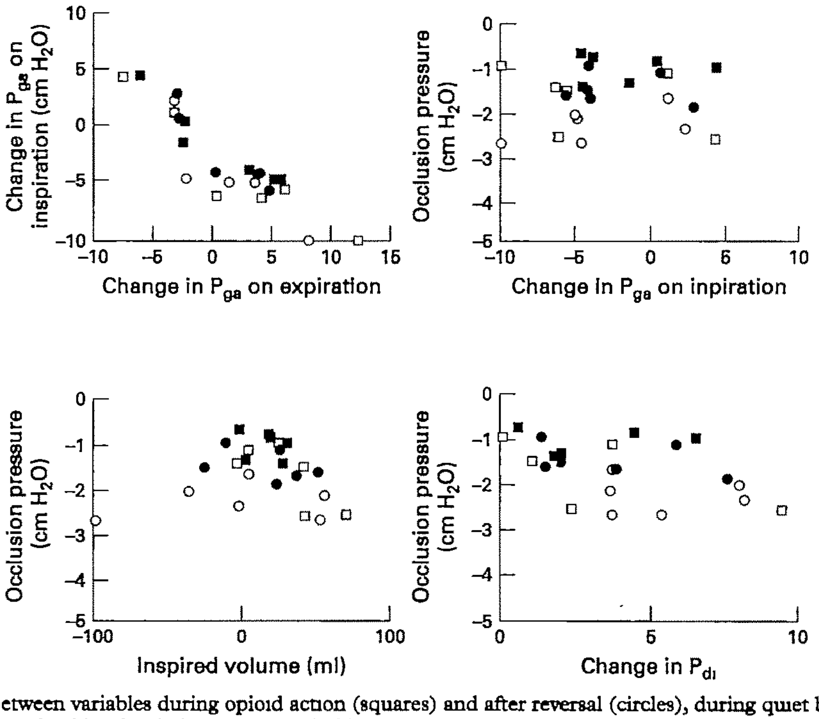

Figure 9 Relationships between variables during opioid action (squares) and after reversal (circles), during quiet breathing (closed symbols) and during carbon dioxide stimulation (open symbols).

Table 19 Covariate analysis showing the likelihood (odds ratio and 95% confidence intervals) of achieving pain control with tramadol (T) compared with fentanyl/Co-codamol (FC)

	Group size (T/FC)	Odds ratio (T/FC)
Up to discharge		
Average	111/117	2.15 (1.02,4.56) (P<0.05)
Maximum	111/117	1.18 (0.69,2.01)
Post-discharge		
Discharge day (average)	83/94	1.99 (1.04,3.79) (P<0.05)
Average (0–3 days)	85/94	1.00 (0.51,1.98)
Maximum (0–3 days)	85/94	1.84 (0.84,4 04)

attributes of potential value in this setting. This study aimed to evaluate its suitability in day surgery.

Two hundred and twenty eight adults scheduled to undergo groin surgery were studied in this prospective, randomized, double-blind study in six United Kingdom centres. They received either tramadol 100 mg or fentanyl 100 µg i.v. at induction, followed by intraoperative increments of up to tramadol 100 mg or fentanyl 100 µg. Standardized general anaesthesia consisted of propofol 2.5 mg kg^{-1} i.v. followed by spontaneous respiration of isoflurane in nitrous oxide and oxygen. Local anaesthesia (1% lidocaine with epinephrine 1:200 000) infiltration or ilioinguinal nerve block was administered. After the operation patients continued, as dictated by the randomization, with either: i.v. or oral tramadol 100 mg (2 capsules); or i.v. fentanyl 100 µg or oral Co-codamol (codeine16 mg/paracetamol 1000 mg) (2 capsules). Morphine was available for rescue analgesia. After discharge, study medication was taken as required 4 hourly, up to 8 capsules in 24 h, and recorded with the pain scores, up to 72 h after discharge, in a diary card and by telephone enquiry. Pain intensity and relief were scored using 4-point and 5-point verbal rating scales respectively.

There were no demographic differences between the two study groups. Covariate analysis shows the likelihood (odds ratio and 95% CI) of achieving good pain control (no/slight pain) for tramadol (T) compared with fentanyl/Co-codamol (FC) (table 19).

There was a two-fold greater requirement for rescue analgesia in the fentanyl/Co-codamol group (8.5% *vs* 4.5%). Thirteen patients were admitted of whom three in the tramadol and five in the fentanyl/Co-codamol groups were for reasons which could be attributed to the analgesic or anaesthetic drugs.

The only statistically significant difference in side-effects was greater somnolence reported in the tramadol group (9% *vs* 3%, P<0.05), but this was not responsible for any admissions.

This study has demonstrated that when the analgesic requirement is highest, on the day of discharge, tramadol is statistically superior to Co-codamol in analgesic efficacy, with an acceptably low incidence of side effects.

Acknowledgement

Searle and Grünenthal kindly provided financial support and study medication for this study.

Keywords: analgesics opioid, tramadol; surgery, day-case

Changes in muscle protein synthesis in rats subjected to caecal ligation and puncture or laparotomy

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The catabolic response to sepsis and tissue injury is associated with muscle wasting, which may delay weaning from mechanical ventilation and prolong rehabilitation. The time course and magnitude of the changes in muscle protein synthesis in these circumstances are poorly defined and there is a need for relevant animal models in which to study potential anabolic agents. We have investigated changes in fractional muscle protein synthesis (Ks, % per day) over time in rats subjected to sepsis (caecal ligation and puncture (CLP)) or tissue injury (laparotomy (LAP)).

Table 20 Muscle Ks was 7.48 (0.25) at the start and 6.45 (0.33)* at the end of the study in control rats. **P<0.0001 compared with control, †P<0.0001 compared with LAP animals

	24 hr	72 hr	96 hr
CLP Ks	3.28 (0.20)**†	2.87 (0.24)**	3 33 (0 21)**
LAP Ks	5.03 (0.39)**	3.25 (0.31)**	2.66 (0.16**

Male Wistar rats, mean weight 256 g, were randomized to produce eight groups of similar mean weight. Three groups of 17 underwent CLP and three groups of 12 LAP, surviving animals being killed at 24, 72 or 96 h. All animals were denied access to food during the study, and housed in wire-bottom cages postoperatively to prevent coprophagia. Twelve rats were killed at the start of the experiment to provide baseline values, and 12 more (housed in standard cages with free access to food) killed at 96 h. Rates of protein synthesis were measured by the "flooding-dose" technique. Ten minutes before death, 150 µmol 100 g^{-1} body weight ^{4}^{3}H-phenylalanine was injected via a tail vein in a volume equal to 1 ml 100 g^{-1} body weight. Animals were killed by decapitation. Gastrocnemius muscles were rapidly dissected out and placed in iced water, at which time it was assumed that protein synthesis had ceased. Fractional rates of protein synthesis (Ks, % age of muscle protein renewed by synthesis per day) were calculated from the specific radioactivities of protein bound and tissue-free phenylalanine in the acid-soluble fraction of the muscle homogenates. Results are presented as mean (SD). Statistical analysis was by analysis of variance (ANOVA) using the Fisher PLSD test.

The changes in Ks are shown in table 20.

Sepsis induces a more rapid decrease in fractional rate of protein synthesis in gastrocnemius muscle of the rat than does laparotomy alone. Subsequently protein synthesis is reduced to a similar extent after the two insults and remains depressed for up to 96 h. This model may prove useful for studying the potential of anabolic agents in severe sepsis.

Acknowledgement

Dr M. J. O'Leary was supported by the Joint Research Board of St. Bartholomew's Hospital, the study was funded by a grant from The British Journal of Anaesthesia and BMI Columbia Healthcare Ltd.

Keywords: model, rat; infection, sepsis; surgery, laparotomy

Solubility coefficients of xenon and nitrous oxide in human blood, saline and olive oil

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The solubility of nitrous oxide in olive oil is traditionally taken as 1.4,[1] but more recently values of 2.2 [2] and 1.63 [3] have been measured by novel methods. We have used a method for the measurement of volatile anaesthetic partial pressures in blood[4] to determine Ostwald solubility coefficients of nitrous oxide in three different media. To justify the adaptation of this method, we have also measured the solubilities of xenon, values for which are better established in the literature.

Ten samples of blood were obtained from starved healthy volunteers and patients undergoing major surgery at induction of anaesthesia. Samples were equilibrated with 70% xenon or 50% nitrous oxide in oxygen in a closed-glass tonometer at 37°C for 1 h. They were then equalized to atmospheric pressure and re-equilibrated for a further 20 min. A 2-ml sample of the fluid was then removed and the partial pressure of anaesthetic in it analysed by a two equilibration headspace technique[4] using a Hewlett Packard 6890 gas chromatograph fitted with a thermal conductivity detector. If the measured partial pressure was within 10% of the tonometer partial pressure, the solubility coefficient was calculated from each equilibration and averaged. Ten such averages were obtained for blood, for normal saline and for extra virgin olive oil (SG 0.908). Results are presented in table 21

The xenon results are in very good agreement with those published previously, leading us to believe that our technique is valid. The value we have obtained for the oil:gas solubility of

Table 21 Ostwald solubility coefficients at 37°C, mean (95% confidence interval)

	Blood:Gas	Saline:Gas	Oil:Gas
Xe	0.13 (0.005)	0.08 (0.003)	1.68 (0.07)
N_2O	0.47 (0.003)	0.39 (0.01)	1.53 (0.07)

nitrous oxide agrees with Snedden's study, and if Meyer and Gottlieb-Bilroth's value from 1921 of 1.4 is actually the Bunsen coefficient[3] (it is unclear from the original text) then it is only Cooper and Joseph's value which is anomalous, and a value of 1.6 may be taken as the solubility of nitrous oxide in olive oil.

Acknowledgement

The gas chromatograph used in this study was made available through a project grant from The Association of Anaesthetists of Great Britain and Ireland.

Keywords: anaesthetics gases, nitrous oxide; anaesthetics gases, xenon; solubility, Ostwald solubility coefficient

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Inspired arterial partial pressure differences of halothane, isoflurane and sevoflurane in rats

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Human studies generally estimate anaesthetic depth from end-tidal volatile anaesthetic partial pressure by assuming that the partial pressure in brain tissues is equivalent to that in arterial blood and hence end-tidal partial pressure. The end tidal-arterial partial pressure difference is small but measureable in humans and large animals and has been attributed to venous admixture, alveolar dead space and the solubility of volatile anaesthetic agent used.[1 2] In small animals the inspired partial pressure is used as an alternative to end-tidal[3] but data are not available for inspired arterial partial pressure ratios. It was hypothesized that in rats the inspired arterial ratio for halothane, isoflurane and sevoflurane would be within the inspired arterial range for larger animals and that the gradient between the inspired and arterial partial pressure would decrease with a reduction in solubility of the agent.

Anaesthesia was induced in 18 female Wistar rats breathing spontaneously either 2% halothane, 3% isoflurane or 4% sevoflurane in oxygen using an enclosed funnel. Both femoral arteries were cannulated and the inspired gas concentrations monitored with a Datex Capnomac II calibrated with a standard gas mixture Selected inspired anaesthetic agent concentrations (as shown in table 22) were maintained for 15 min after which 0.5 ml of arterial blood was sampled for estimation of anaesthetic agent partial pressure using our technique of two-stage head space analysis calibrated with standard gases[4] and developed for small-sample size.The results show no significant difference between halothane and isoflurane but sevoflurane, the least soluble agent, demonstrates significantly less difference between inspired and arterial partial pressures ($P<0.0001$).

Keywords: anaesthetics volatile, halothane; anaesthetics volatile, isoflurane; anaesthetics volatile, sevoflurane; monitoring, partial pressure

Table 22 The inspired–arterial partial pressure differences expressed as arterial:inspired ratios (mean (SEM)) for halothane, isoflurane and sevoflurane in rats at different inspired concentrations. There is no significant difference in results within the halothane, isoflurane and sevoflurane groups (ANOVA)

Anaesthetic agent	0.8%	1%	1.2%	1.4%
Halothane	0.60	0.68	0.65	0.64
(*n*=6)	(0.04)	(0.05)	(0.04)	(0.04)
	0.8%	1.2% (*n*=5)	1.6%	2%
Isoflurane	0.54	0.58	0.61	0.61
(*n*=6)	(0.06)	(0.06)	(0.07)	(0.06)
	1.5%	2%	2.5%	3%
Sevoflurane	0.72	0.86	0.82	0.79
(*n*=6)	(0.05)	(0.07)	(0.06)	(0.06)

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Propofol or sevoflurane for laryngeal mask airway insertion

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We compared the conditions for laryngeal (LMA) insertion obtained by either vital capacity breath inhalational induction of anaesthesia with sevoflurane or i.v. induction with propofol.

Eighty-eight patients, aged 18–65 yr, ASA status I–II, undergoing general anaesthesia for elective orthopaedic, gynaecological, or plastic surgery where use of the LMA was indicated, were randomized into two groups in a prospective, single-blinded study. Patients in Group P ($n=44$) received i.v. propofol 3 mg kg^{-1} mixed with 2 ml of 1% lidocaine over 25–30 s. Patients in Group S ($n=44$) had a modified vital capacity breath technique inhalational induction with 8% sevoflurane in 50% nitrous oxide and oxygen. No opioids were given. Ventilation was not assisted. LMA insertion was attempted at 1-min intervals from the start of induction (time zero) in each group. Additional propofol (1 mg kg^{-1}) was given if unsuccessful in Group P after 2 min and for significant adverse responses in Group P and Group S which did not settle spontaneously.

The median time to successful LMA insertion was 1.3 min in the propofol group and 2.2 min in the sevoflurane group, $P< 0.05$. The number of patients in which the LMA was successfully inserted at 1 min was 8 (18%) in the S group compared with 29 (66%) in the P group, $P<0.05$; at 2 min, 22 (50%) in S compared with 11 (25%) in P; and at 3 min 14 (32%) and 4 (9%) in S and P respectively, all $P<0.05$. All patients had the LMA successfully positioned by 3 min. The incidence of cough, gagging, and laryngospasm at 1 min were less in P than S group, 2 (4.5%) compared 10 (22%), 8 (18%) compared with 18 (40%), 3 (6.8%) compared with 11 (25%) respectively, all $P<0.05$. By 3 min the incidence of these adverse responses was zero in S. There was no difference between the two groups for head movement, and limb movement was less in S than P, 11% compared with 45%, $P<0.05$. In Group P, 11 (25%) required additional propofol compared with 4 (9%) in Group S, $P<0.05$. The median duration of apnoea was 25 s (range 0–45) in S compared with 55 seconds (range 35–90) in P, $P<0.05$.

In conclusion, vital capacity breath inhalation induction with 8% sevoflurane in 50% nitrous oxide and oxygen provides comparable conditions to propofol alone for LMA insertion, however, the median time to achieve this being 2.2 min with sevoflurane compared with 1.3 min with propofol.

Keywords: anaesthetics volatile, sevoflurane; equipment, masks anaesthesia

Comparision of the respiratory effects of sevoflurane and halothane in infants and young children

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Developmental aspects of the respiratory system during early life may predispose infants to greater respiratory depression during anaesthesia than older subjects.

Infants were randomized to receive 1MAC halothane (HA) or sevoflurane (SA). Flow, pressure (P_{ao}), end-tidal carbon dioxide (P_{α,CO_2}) and respiratory inductive plethysmography (RIP), calibrated with the qualitative diagnostic calibration (QDC) method, were measured during spontaneous ventilation and airway occlusions. Tidal volume (V_T), minute ventilation (V'_E) and respiratory rate (RR) were measured. Respiratory drive was assessed with $P_{0.1}$, the P_{ao} at 100 ms of an occluded inspiratory effort. The time to peak tidal inspiratory (t_{PTIF}) and expiratory (t_{PTEF}) flow; and the inspiratory (C_I) and expiratory (C_E) centroids were expressed as a percentage of the inspiratory (t_I) and expiratory (t_E) time. The phase relation of RIP ribcage and abdomen (PhRTB) was also calculated. Differences in the group means were assessed with unpaired *t*-tests and calculation of the 95% confidence intervals (CI) of the difference (* $P<0.05$).

Fifteen infants in both the SA and HA groups were studied: mean age 14.5 and 14.6 months, weight 11.1 (SD 2.6) and 10.0 (SD 1.7) kg respectively. Respiratory depression was significantly greater in the SA group evidenced by a lower V'_E and RR. The inspiratory flow waveform was skewed to the right and that of the expiratory to the left in the SA group. There was no difference in respiratory drive evidenced by similar $P_{0.1}$. Thoraco-abdominal asynchrony was less in the SA group evidenced by the lower PhRTB. (Results expressed as mean (SD)) (table 23).

Table 23 Differences in group means assessed by unpaired *t*-tests and 95% confidence intervals (CI). *$P<0.05$

	Sevoflurane	Halothane	Difference SA-HA (95% CI)
P_{a,CO_2} (kPa)	6.1 (1.0)	6.0 (0.9)	0.12 (−0.59, 0.83)
V'_E (l/m²)/min	4.5 (1.1)	5 4 (0.8)	−0.9 (−1.60, −0.12)*
V_T (mL⁻¹ᵏᵍ)	5.5 (0.8)	5.5 (0.7)	0 (−0.6, 0.6)
RR (bpm)	37.5 (7.2)	46.7 (8.5)	−9.0 (−15.2, −3.2)*
t_{PTIF}/t_I (%)	53.3 (9.8)	42.1 (6.1)	11.2 (4.9, 17.4)*
t_{PTEF}/t_E (%)	22.0 (7.0)	31.0 (10.0)	−9.0 (−16.0, −2.0)*
C_I/t_I (%)	53.0 (6.0)	48.0 (2.0)	5.0 (2.0, 8.0)*
C_E/t_E (%)	37.0 (9.0)	45.0 (3.0)	−8.0 (−13.0, −3.0)*
$P_{0.1}$ (kPa)	0.50 (0.35)	0.61 (0.26)	−0.11 (−0.36, 0.14)
PhRTB (%)	28.1 (14.5)	44.5 (12.9)	−16.4 (−28.2, −4.6)*

The greater respiratory depression during 1MAC SA than HA in infants while statistically significant may not be clinically important. Differences in the shape of the inspiratory flow waveform and PhRTB suggest that the recruitment of respiratory muscles during SA and HA differ.

Acknowledgement

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Keywords: anaesthetics volatile, sevoflurane; anaesthesia, paediatric; ventilation, effects

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Succinic acid causes hyperexcitability in normal and one paramyotonia congenita-mutant muscle sodium channel

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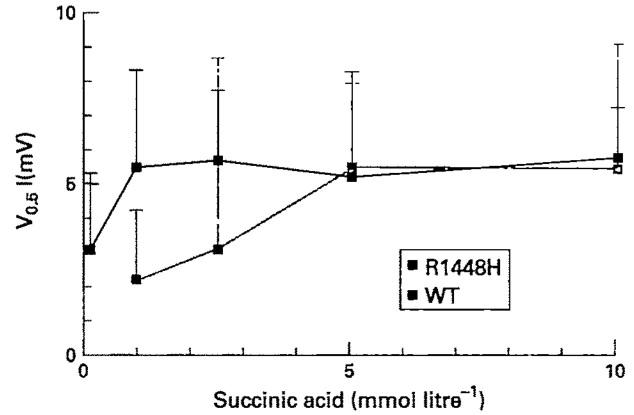

Figure 10 Effect of succinic acid on $V_{0.5}$.

Recently it has been shown that succinylcholine application on the extracellular surface of HEK293 cells expressing either wild type (WT) α-subunit of the adult human muscle sodium channel or paramyotonia congenita-mutant R1448H exerts small inhibitory effects on mutant channel function.[1] These inhibitory effects cannot explain adverse reactions after suxamethonium administration in myotonic patients, for example, masseter spasm.[2] Therefore it was the aim of this study to investigate possible excitatory effects of one succinylcholine breakdown-product succinic acid on normal and R1448H-mutant sodium channel function.

WT and R1448H-mutant α-subunits of human muscle sodium channels were heterologously expressed in human embryonic kidney (HEK293) cells. Standard whole-cell voltage clamp experiments [3] were performed at 20°C in a stream of bath solution for control and wash-out experiments and in 10 mmol litre⁻¹, 5 mmol litre⁻¹, 2.5 mmol litre⁻¹, 1 mmol litre⁻¹ and 0.1 mmol litre⁻¹ succinic acid. For data acquisition and further analysis, we used the EPC9 digitally controlled amplifier in combination with pulse and pulse-fit software. For steady-state activation, families of depolarizing test pulses were applied from a holding potential of −100 mV to −50 mV, −45 mV and so on in 5-mV increments up to +45mV. The resulting normalized conductance-voltage-plots were fitted to a Boltzmann equation yielding the voltage at half-maximum conductance ($V_{0.5}$) and the slope factor z_δ. For statistical evaluation, test data were compared with control data obtained in the same time interval after seal formation in bath solution according to the method of multiple comparisons with *a priori* ordered hypotheses [4] by means of Mann–Whitney *U* test $P<0.05$ was considered significant.

Succinic acid shifted normal (WT) and R1448H-mutant $V_{0.5}$ in the hyperpolarizing direction. Figure 10 shows mean $\Delta V_{0.5}$ (+SD) (mV) *vs* succinic acid concentration (mmol litre⁻¹). In R1448H, succinic acid effects were significant in comparison with controls down to a concentration of 5 mmol litre⁻¹, in WT down to a concentration of 1 mmol litre⁻¹. All shifts depicted in figure 10 were successfully washed out.

The hyperpolarizing shift of $V_{0.5}$ caused by succinic acid means hyperexcitability resulting from activation of a greater number of channels at more negative test potentials in WT and R1448H channels. This effect was even more pronounced in WT.

Acknowledgement

We are indebted to Professor Lehmann-Horn / Ulm for providing us with transfected cells.

Keywords: ions, sodium; pharmacology, succinic acid

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British Journal of Anaesthesia 1998; **80**: 562–567

CORRESPONDENCE

Anaesthesia and the competence revolution

Editor,—In the recent editorial on anaesthesia and the competence revolution,[1] Dr Greaves summarized clearly the problems involved in the assessment of doctors, and warns of the dangers inherent in following a vocational approach to the assessment of anaesthetists. However, as Dr Greaves writes, practical skills, behaviour and personal qualities are important requisites for an effective anaesthetist. So how best can we assess these aspects? It is clear that a "competency" approach, dividing the process of anaesthesia into a series of simple tasks, the performance of which is marked and collated, is not appropriate. Such an approach trivializes professional behaviour, with its complex underlying reasoning, and makes no effort to assess these deeper aspects.

Yet it is clearly vital to examine performance in the workplace. The Standing Committee on Postgraduate Medical and Dental Education (SCOPME), whose role includes advising the Secretary of State on such matters, recognizes the need for service-based assessment. It suggests that such assessment should be a formal process with right of appeal, and should be fair, but not too bureaucratic or legalistic. Furthermore, it should be part of the learning process.[2]

Standards remain a problem. Using specific laid down criteria for each aspect of anaesthetic performance (*criterion* referencing) is one possibility. However, such an approach would be over complicated, requiring frequent revision of criteria used, and would not assess those deeper aspects of behaviour that we would wish to examine. Relating performance to that of others, regardless of the actual standards achieved (*peer* or *norm* referencing) is another, albeit unsatisfactory, approach.

However, a third method, relating the standard of performance to the assessor's expert understanding of the minimum required for safety (*limen* referencing) could provide the basis for a workplace-based assessment standard.[2] Such an approach has been found to be useful and reliable.[3] Although it is difficult to quantify the element of professional judgement involved, there is currently no better method of assessing performance of the whole task.[4] Consensus opinion on standards is difficult to attain, but the main underlying issue must be one of ensuring the relative safety of the clinical practice of the trainee given that person's stage of training and level of supervision. Consultant anaesthetists are well aware of what constitutes safe practice. By a continuing dialogue with the trainee, they are able to get a good idea of the underlying thought processes, attitudes, skills and knowledge, and provide feedback to the trainee. With appropriate safeguards, such judgmental elements within an array of assessments and assessors will strengthen rather than weaken the accuracy of the picture.[4] Such safeguards might include full documentation, openness and right of appeal. It is helpful to avoid the use of graded assessments, because such an approach is highly subjective and lends a spurious objectivity to the assessment.[5]

To write, as Dr Greaves has in his concluding paragraph, that "until the time that research is done, measurements made in the workplace should not be used either to monitor the progress of trainees or make decisions in relation to their careers" is clearly wrong. After all, there is also a relative lack of quantitative research-based knowledge supporting the effectiveness of the medical education we provide, yet we would certainly not choose to *stop* providing any education on this basis.

There is no single ideal assessment method, and it is unlikely that there ever will be. Each method used will have different advantages, disadvantages, reliability, validity and feasibility. A range of methods must therefore be used, in the knowledge of each one's strengths and weaknesses. These will develop and become refined in the light of experience.

The South Thames (E) Assessment Scheme is an example of one such scheme which is evolving in the full knowledge of the problems associated with workplace-based assessment, providing valuable feedback to trainee and trainer alike. The real danger lies in *not* performing assessments in the workplace. Without them, the Record of In-Training Assessment (RITA) system of Annual Review, upon which our whole system of specialist accreditation relies, becomes a worthless paper exercise.

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Editor,—I read with interest Dr Greaves' editorial on the shift towards competence-based education.[1] While this educational strategy has many obvious attractions he highlights some of the problems likely to be encountered if the approach is adopted more widely. In particular he alludes to the difficulties associated with competence-based assessment. I agree fully with his assertion that our understanding of the tools and assessment process currently available are inadequate to justify their introduction and would like to comment further.

The fundamental role of assessment in the learning process is often not fully appreciated. While assessment in the form of traditional examinations has often been used primarily as a means of arbitrarily discriminating between candidates, a more enlightened approach to assessment views it as a crucial and inherent part of the learning process itself. For instance it is not surprising that what students choose to learn is largely assessment-driven—candidates concentrate on areas in which they expect to be examined. Assessment can also pinpoint weak points allowing remedial work. Crucially the assessment process can act as an appraisal of the teaching system itself. A major difference likely to occur with the use of competence-based assessment is the use of criterion-referenced marking strategy. Traditional examinations have often been perceived as being norm-referenced with the overall performance of an individual related not only to his own performance but also to that of other candidates with a pass mark being set such that an arbitrary percentage of candidates are successful. This is in marked contrast with criterion-referenced assessment. In this case a candidate is deemed competent and passes the assessment if pre-determined minimum standards of performance in specified areas are met. This is analogous to the driving test in which success depends wholly on carrying out hill starts emergency stops, etc, safely and is not related to the driving abilities of other learner drivers. While this approach seems inherently fairer for the candidate there may be greater fluctuations in the number of successful candidates at different examination sittings which could have implications for the new training system in anaesthesia.

While any assessment process requires considerable forethought, design and planning, competence-based assessment is particularly complex. Madsen and colleagues[2] have described the clinical competency criteria they use for assessment of anaesthetic trainees; these fall into four broad categories—knowledge, case management, technical skills and oral skills. They also describe "essential character attributes" which include ethics, reliability and appropriate response to stressful situations.

Gonczi[3] has described the process needed to design the more exhaustive competency-based assessment used by the Royal Australian College of General Practitioners. Briefly the first step was to analyse the competencies needed by a GP; these included knowledge, skills and attitudes relevant to the medical areas and problems to which they were directed. It was deemed necessary to assess knowledge, interpretative skills, problem solving attitudes interpersonal and communicative skills, and perceptual abilities. These areas are not assessed in isolation. Instead the use of these competencies in solving a variety of problems in different situations is considered. The different areas also receive different weightings in the assessment. In order to carry out this assessment of candidates' competence, eight different assessment methods were needed—case commentaries, MCQs (including simple completion sequential and relationship analysis questions), clinical interpretation tests, computerized case studies, physical examination, diagnostic interview, management interview and in-practice assessment. These examples illustrate not only the complex nature of competence-based assessment but the need for a broad range of methods of assessment to increase both the validity and reliability of the process.

The design of effective competence-based assessment in anaesthesia undoubtedly needs further research resource allocation and probably the involvement of professional educationalists. There is perhaps a danger of being swept along by the tide of change brought by the medical education revolution. However, to adopt newer approaches without the resources research, and experience needed to properly implement them would be ill advised.

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Autologous blood transfusion

Editor,—We read with interest the commentary on the guidelines for autologous transfusion.[1] In particular it states that blood containing amniotic fluid should not be salvaged because of the risk of embolism and disseminated intravascular coagulation (DIC). We agree with this. However, the risk–benefit ratio of transfusing salvaged blood that might contain small amounts of amniotic fluid has to be considered.

A 26-yr-old Jehovah's Witness developed progressive haemorrhagic shock secondary to acute haemoperitoneum, 6–8 h after emergency Caesarean section under general anaesthesia for fetal distress. At Caesarean section the obstetrician had experienced moderate difficulty in separating the placenta from the uterine wall and blood loss had been estimated at 800 ml. As resuscitation commenced with oxygen, i.v. crystalloid and synthetic colloids, extensive discussion took place with the patient as to what form of transfusion (if any) would be acceptable to her. She concluded that transfusion of autologous blood was acceptable (even if it was temporarily out of circulation) but that homologous transfusion (whether red cells, platelets or fresh frozen plasma) was not.

Haemoglobin concentration before Caesarean section and after initial resuscitation decreased from 12.9 to 6.6 g dl^{-1}. Laparotomy was performed 9 h after Caesarean section at which 1400 ml of blood were salvaged from the peritoneal cavity. Blood was prepared using a red cell salvage centrifugal processor (Cell Saver 3 Plus Haemonetics) suspended in 0.9% saline solution and reinfused. Immediately after the second operation haemoglobin concentration was 5.9 g dl^{-1} but this had decreased to 3.7 g dl^{-1} within 12 h with further bleeding. Another 200 ml collected from the abdominal drains over this time were reinfused with an increase in haemoglobin concentration from 3.8 to 7.7 g dl^{-1}, but this was transient, decreasing to 4.0 g dl^{-1} in 6 h.

Coagulopathy and thrombocytopenia developed before laparotomy and peaked 12 h after operation (INR 2.5, APTT ratio 2.5, platelets 53×10^9 $litre^{-1}$). Tissue hypoxia was manifested as lactic acidosis (base deficit 8.1 mmol $litre^{-1}$ 12 h after operation) and oliguric renal failure (urea 16 mmol $litre^{-1}$, creatinine 0.31 mmol $litre^{-1}$, 2 days after operation).

Methods used to minimize blood loss and maximize oxygen delivery included: sedation and controlled ventilation for 36 h; central venous and direct arterial monitoring (during and after operation) to guide volume expansion; maintenance of arterial Po_2 greater than 25 kPa; aprotinin; small infrequent blood samples; early enteral nutrition, iron, folic acid and vitamin B_{12} supplements; and recombinant human erythropoietin (4000 u. s.c once daily for 5 days).

The patient was discharged from the intensive care after 6 days with a haemoglobin concentration of 4.7 g dl^{-1} and left hospital 3 days later expressing the wish to have another child. By day 43 her haemoglobin concentration had increased to 9.8 g dl^{-1}.

It is impossible to know the contribution which the salvaged blood made to the postoperative course. It undoubtedly increased haemoglobin concentration at a stage when oxygen delivery was critical. However, whether the reinfused red cell suspension contained a clinically significant amount of amniotic fluid is unknown. This may have been one of several factors contributing to DIC. Would it have been possible to analyse the salvaged blood–red cells for amniotic fluid both qualitatively and quantitatively before reinfusion and if so could this have aided management?

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1. British Committee for Standards in Haematology Blood Transfusion Task Force. Guidelines for autologous transfusion. II. Perioperative haemodilution and cell salvage. *British Journal of Anaesthesia* 1997; 78: 768–771.

Propofol and electrophysiological variables during emergence from anaesthesia

Editor,—We read with interest the article by Doi and colleagues[1] showing relationships between calculated concentrations of propofol and several variables. However, the original data are not described in enough detail to enable a knowledgeable reader to verify the reported results. From a statistical standpoint the article had two major flaws: (i) linear relationships were computed using repeated measurements in 10 patients leading to a medley of 349 points; (ii) linear prediction bands were shown as straight lines.

The first misuse of simple linear regression was to mix repeated measures in just a few patients. When simple linear regression is used to model the data, hypotheses behind the model must be kept in mind (i.e. the independence and Gaussian distribution of the error terms). In other words pooling repeated measures which are obviously non-independent is misleading. Some techniques have been developed to cope with the pooling of independent data from several individuals with non-independent repeated measures in the same individual.[2]

The second misuse of statistical tools was to draw linear prediction bands which are curvilinear in essence.[3 4] Moreover, the prediction band is usually used for prediction for an individual and the computation made by the authors based on 349 measures in 10 patients is misleading because of the non-zero covariance between the repeated measures made in each individual.

As pointed out by Shann,[5] the moral of this story is that we should never use a statistical technique unless we are completely familiar with it.

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Editor,—Thank you for the opportunity to reply to the comments of Professor Cantraine and Dr Mélot. A treatment to prevent repeat myocardial infarction in 90% of patients would be hailed deservedly as a major therapeutic advance. However, an induction agent which was successful in only 90% of patients would be considered to be completely useless. Even one which was 99% successful would fail to meet the unique requirements of anaesthetists for total success. The same type of reliability must be applied to a technique of measuring the effect of anaesthetics on patients during surgery. A system which could reliably detect transition from unconsciousness to consciousness successfully in 99% of patients would have the possibility of providing incorrect information in one of every 100 patients who received an anaesthetic. Even one which was unsuccessful in only one of 1000 patients would be of little use.

The prediction bands did not demonstrate confidence intervals which would have been curvilinear but were calculated from residual variance from the regression line and were presented to demonstrate the distribution of the EEG variables. Had the 95% confidence intervals been calculated before regression, they would have been curvilinear. Each figure contained data from identical patients and the essential point of the study was that a real difference was detected in the performance of the monitoring systems during the recovery phase. It may be true that Poon's statistical method could be more valid for computing linear relationships from repeated non-independent measurements in multiple subjects. Poon's method can reputedly detect mild non-linearities. However, if our data were subjected to Poon's analysis the results would not be much different as experimental conditions were similar among subjects and linear regression analysis probably dealt with our pooled, non-independent measurements appropriately. Additionally, our data were Gaussian in distribution as analyses of other data from our studies showed the AEPI and BIS to be normally distributed. Therefore, inter-individual variability would have had far less effect on the analysis. In any case we believe this criticism in no way affected our conclusions about the AEPI as we found it to be the worst predictor of propofol concentration.

While we agree that a statistically puristic approach may have been to adopt the analysis suggested by our statistical colleagues, we considered that our approach would be a greater test of the systems under evaluation and may yield a higher level of confidence in the use of the different EEG variables. It is important that we do not accept a system to assess the level of anaesthesia which appears to be statistically sound if this does not provide the necessary extremely high level of clinical reliability. Figure 1 clearly demonstrated the considerable overlap in BIS values recorded during the transition from unconsciousness to consciousness. This was repeated with all variables except $\text{AEP}_{\text{index}}$ which showed almost total separation between values recorded before and after awakening. The use of curvilinear 95% confidence intervals would have included a wider range of data points at the extremes, would have added no additional value to the analysis and may have been less stringent in presenting the data. The moral of this story is that statisticians may contribute less to an understanding of medical matters than they realize.

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Bronchospasm during inhalation of nebulized midazolam

Editor,—Nebulized midazolam has been described previously in a pilot study of adult volunteers in which it was administered nasally.[1] We would like to report a complication of nebulized midazolam administered orally via a jet nebulizer.

During the course of an investigation into the sedative effects of nebulized midazolam, two of 10 subjects complained of chest tightness. Both were healthy volunteers although one gave a history of childhood asthma. The preparation of midazolam 5 mg ml^{-1} i.v. (Hypnovel, Roche) was administered in a dose of 0.2 mg kg^{-1} via a jet nebulizer (Pari LC Plus, Pari Medical Limited). Changes in the ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) were measured and were greater in these subjects than in the remaining volunteers (table 1). Oxygen saturation values were measured throughout the study and decreased with increasing sedation; the lowest value for the 10 volunteers was 93%, occurring in one subject who remained asymptomatic and in one who developed chest tightness.

Alternative routes of administration of anaesthetics and anaesthetic adjuvants are constantly being sought with the aim of increasing convenience, safety, bioavailability and effective drug action while decreasing side effects and cost.[2] Intranasal midazolam has been used successfully for sedation of children,[3] but causes nasal burning, irritation and lacrimation during instillation into the nares.[4] Nebulized midazolam may offer a more comfortable route of administration but its effects on lung function have not been reported in human subjects. It is known that acidic aerosols may cause bronchoconstriction in asthmatic subjects, particularly if the aerosol is hypotonic or hypertonic,[5] or in the presence of inflamed and hyper-responsive airways.[6] The pH of the preparation of midazolam we used was 3.0 and it is possible that bronchoconstriction could be avoided if a buffered solution were used.

The concept of a nebulized sedative may at first seem an attractive alternative to the parenteral route, especially in children, and a nebulizer may be well tolerated, particularly by an asthmatic child. However, we would advise caution in the use of midazolam by this route, especially where a history of asthma is given, until further studies have evaluated this mode of administration.

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1. Hodgson PE, Woods KM, Bromley LM. Administration of nebulized intranasal midazolam to healthy adult volunteers: a pilot study. *British Journal of Anaesthesia* 1994; 73: 719P.

Table 1 Forced expiratory volume in 1 s (FEV_1) as a percentage of forced vital capacity (FVC) before and 10 min after administration of nebulized midazolam in 10 volunteers

Subject No.	Symptoms of chest tightness	FEV_1/FVC (%) before nebulizer	FEV_1/FVC (%) after nebulizer	Percentage change in FEV_1/FVC (%)
1	No	81.3	84.4	3.93
2	No	93.0	92.9	−0.15
3	No	78.2	76.9	−1.61
4	No	92.3	92.1	−0.22
5	No	81.8	83.0	1.48
6	No	81.6	78.8	−3.42
7	No	88.2	82.6	−6.34
8	No	89.2	85.3	−4.37
9	Yes	70.0	60.0	−14.29
10	Yes	82.2	72.2	−12.16
Mean		83.8	80.8	
Confidence interval (%)		4.36	5.99	

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Editor,—Thank you for the opportunity to reply to the comments of Drs McCormick and Thomas regarding nebulized midazolam. They refer to our pilot study using nebulized midazolam for sedation in adults.[1] In this study we enrolled 15 healthy adult volunteers, all of whom were non-smokers and had no current or previous cardiorespiratory history. I note that one of the volunteers in Dr McCormick's study had a history of childhood asthma. In our study midazolam was administered using 100% oxygen via a "Cirrus" single-use adult nebulizer mask (Intersurgical Ltd) with the manufacturer's recommended flow rate of 7 litre min^{-1}. This is said to deliver a mean particle size of 3.5–5 μm in diameter. The size of the particles is the main determinant of the anatomical site of drug deposition.[2] It is expressed as aerodynamic mass median diameter (AMMD).[3] Deposition of particles is proportional to the square of the AMMD. Only particles less than 12 μm can reach the alveolar region. At 4 μm, more than 60% of particles are filtered by the upper airway in nasal breathing. In contrast, mouth breathing allows most 2 μm particles past the extra-thoracic airway to reach the alveoli. When a nasal nebulizer is used in adults, 22% of the total dose in the mask is deposited in the nose, irrespective of the nasal breathing pattern.[4] With the nebulizer we used we would predict that 60% of particles inhaled would be trapped in the nose and with some being deposited in the upper airways. The proportion of particles which reach the bronchi is likely to influence the incidence of bronchospasm and it may be that the performance of the nebulizer used in Drs McCormick and Thomas's study differed from the one we used.

In our study the midazolam i.v. formulation was made up to a total volume of 6 ml with saline. Although I am unable to give a precise pH for this solution I believe it is similar to commonly administered nebulizer solutions but I am prepared to accept that a low pH may precipitate bronchoconstriction.

In our adult volunteers there was a high level of acceptability for this method of administration of midazolam. Despite this, after our pilot study we have not pursued the method further. I accept Drs McCormick and Thomas's conclusions that a history of asthma should lead to caution in administering midazolam via a jet nebulizer.

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Low-dose naloxone in the treatment of urinary retention during extradural fentanyl causes excessive reversal of analgesia

Editor,—Urinary retention is a complication of the use of extradural opioids.[1] The mechanism is thought to be inhibition by opioids of sacral parasympathetic outflow, although a supraspinal inhibitory effect at the level of the pontine micturition centre has been proposed.[2] Rawal and colleagues demonstrated a rapid decrease in detrusor muscle function after injection of extradural morphine in volunteers.[3] The effect of morphine on detrusor muscle function in this group was antagonized by administration of naloxone. Husted and colleagues also demonstrated antagonism of the effects of extradural morphine on bladder dysfunction with administration of naloxone 0.4 mg in patients after hysterectomy.[4] Interestingly, the urinary effects were antagonized without reversal of analgesia. This lack of reversal of analgesia was also noted after administration of naloxone 5 μg kg^{-1} h^{-1} to patients receiving extradural morphine after abdominal surgery.[5]

Fear of delayed respiratory depression with hydrophilic opioids has led to a reduction in the use of morphine for extradural analgesia. More commonly a mixture of a lipophilic opioid (fentanyl or diamorphine) with very low concentrations of local anaesthetic is used.[6] Therefore, we evaluated the use of low-dose naloxone for the treatment of urinary retention in thoracotomy patients receiving thoracic extradural fentanyl for postoperative analgesia. After obtaining approval from the Ethics Committee, 30 patients received an extradural bolus of 0.1 ml kg^{-1} of a mixture of fentanyl 10 μg ml^{-1} and 0.1% bupivacaine. This was followed by infusion at a rate of 0.1 ml kg^{-1} h^{-1} of the same mixture. Those patients (n=9) who had not passed urine the morning after operation were allocated randomly to receive either naloxone infusion 5 μg kg^{-1} h^{-1} for 1 h or an equal volume of normal saline infused over the same period. Pain score using a 0–10-cm linear visual analogue scale was recorded at the start of infusion of naloxone and every 15 min thereafter. If the subsequent pain score increased by 3 cm or more above baseline, a bolus of 5 ml of the extradural mixture was given.

The incidence of urinary retention in this population was 30% (n=9). Pain score increased by more than 3 points at 30 min after commencement of infusion (total dose of naloxone received=0.2 mg) in all five patients in the naloxone group. In one patient, pain score increased from 1 to 10 and remained at 9 despite three 5-ml extradural bolus doses. There was no change in pain score in the four patients who received saline. None of the patients passed urine during infusion of naloxone or saline or in the subsequent hour. Based on these early results we abandoned the study

A change in pain score as a result of extradural catheter migration is unlikely. All extradural catheters were sutured to the skin. The temporal relationship between the start of naloxone infusion and increase in pain score and termination of naloxone infusion and decrease in pain score also supports correct catheter position. Although bolus doses of naloxone have been recommended to reverse the side effects of extradural morphine, our concern over the potential for reversal of analgesia led us to choose a low-dose infusion over 1 h.[7] None the less, reversal of analgesia in our patients was rapid and unpleasant. This appears to be markedly different to the published experience with extradural morphine. In support of our experience, Gueneron and colleagues noted partial reversal of extradural fentanyl analgesia with naloxone 0.2 mg i v. followed by infusion of 5 μg kg^{-1} h^{-1} after lithotripsy.[8]

The difference between extradural morphine and fentanyl may be caused by different study populations (i.e. our study investigated thoracic rather than abdominal operations) or by the different lipid solubilities of the two drugs. Fentanyl being more lipophilic than morphine may have a greater systemic component to its analgesic effect and may thus be more susceptible to reversal by naloxone. In patients receiving thoracic extradural analgesia, we found previously no difference in pain scores 4 h after operation and thereafter between infusion of a mixture of fentanyl 10 μg ml^{-1} and 0.1% bupivacaine and fentanyl 10 μg ml^{-1}.[9] Reversal of analgesia with naloxone again supports the importance of fentanyl in thoracic extradural analgesia.

In summary, even very low doses of naloxone can reverse the analgesic effect of extradural fentanyl. Naloxone would appear to have no place in the management of non-life threatening side effects related to this analgesic technique.

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Extradural catheter-related infections in patients with infected cutaneous wounds

Editor,—Bengtsson, Nettelblad and Sjoberg[1] described severe extradural infections in three patients who had infected cutaneous wounds in the lower limbs and suggested that extradural analgesia with catheter placement was unsafe in such patients.

Continuous extradurals for postoperative or post-trauma analgesia are common. Therefore, it is likely that a significant proportion are inserted in patients who develop superficial wound infection. Extradural infections are however relatively rare. It is surprising to have three severe cases reported from one institution. Unfortunately, studies or case reports on extradural infections do not generally cite the location or method of making up the extradural solutions.

It has been demonstrated that the environment in which solutions of drugs are made up is the most important variable affecting the microbial contamination rate.[2] A study of contamination of syringes prepared by trained nurses using a standard aseptic technique in the usual i.v. area of a ward found a 15% contamination rate. There was no contamination when pharmacy personnel performed the same procedure in a clean room with full protective clothing (personal communication, unpublished data). It has been suggested that the risk of infection may be reduced by maintaining a closed system for the duration of the infusion.[3]

Contamination of analgesic solution may be a significant causative factor in extradural infections, particularly where small volumes of analgesic solutions are repeatedly made up in ward areas In this scenario aseptic technique may be imperfect and there is ample potential for contamination of the extradural infusions with pathogens.

In our institution more than 3000 extradurals have been performed for postoperative or post-trauma analgesia and we are yet to experience a case of extradural space infection, although inflammation at the insertion site and culture of skin organisms from catheter tips are common. The extradural solution we use consists of commercially produced sterile 500-ml bags of dilute bupivacaine to which opioid is added in a laminar flow sterile production facility in the hospital pharmacy by trained staff. The delivery system is attached in theatre recovery at the time of extradural insertion and its integrity is generally not broken until removal. Using 500-ml bags ensures that few patients require connection of a second bag. We believe that this is an optimal system for avoiding infection caused by solution contamination.

It is well established that TPN infection rates are minimized by limiting disconnection and reconnection of the delivery systems. The same considerations may apply to continuous extradural infusion. It would be unfortunate if the potentially erroneous conclusion of the case report leads to patients being deprived of extradural analgesia in this clinical setting.

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Editor,—We were interested in the suggestion that the extradural infections we described[1] might emanate from contamination introduced into the extradural space when preparing the transfusion system. First, we would like to clarify that in the three cases presented, the spinal space infections occurred at different hospitals and the extradural catheters were administered by three different anaesthetists. Although we cannot exclude with certainty the possibility that the infections were introduced by the transfusion system, this seems from our point of view unlikely. In the cases described the extradural infusions were not made up at the bedside but in a pharmacy area located close to the ward nurse office. Furthermore, the extradural infusions were administered via a bacterial filter (Portex) and the transfusion systems and anaesthetic solutions were changed every 12 h. Therefore, we believe that contamination of the transfusion systems is less likely. Furthermore, the bupivacaine solutions used in these three patients had a bacteriostatic or even bactericidal action.[2,3]

Although we agree that the handling of the extradural solutions described appears theoretically appealing, the finding of a lack of spinal space infections in 3000 postoperative extradurals (it is not stated if these patients had infected cutaneous wounds) has little relevance as the common prevalence could be as low as 1 in 50 000.[4] Therefore, at least several 100 000 extradurals are needed in order to obtain a material large enough for conclusions to be made on the adequacy of the preparatory technique of the extradural infusion.

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Editor,—I read with interest the articles by Jakobsen, Christensen and Carlsson,[1] and Bengtsson, Nettelblad and Sjøberg,[2] and wish to present a case of a 67-yr-old patient who presented a management problem pertinent to the articles mentioned.

The patient was a poorly controlled insulin-dependent diabetic (Hb A1c 10.2) with a history of controlled atrial fibrillation, hypertension, dilated cardiomyopathy and a symptomatic hiatus hernia. She presented to the vascular surgery department with a necrotic pre-tibial venous ulceration that was obviously infected. A surgical debridement was performed under intrathecal anaesthesia which was uneventful. After operation further necrotic areas appeared requiring further debridement which was again performed under intrathecal anaesthesia. Wound cultures confirmed *Pseudomonas* and *Proteus* growth and the patient was started on Timentin i.v. She was apyrexial and had negative blood cultures before starting antibiosis. But the wound necrosis continued to spread and a plan for multiple consecutive daily debridements and skin grafting was made. The surgeons estimated that 10 or 12 procedures would be necessary.

The patient's admission was complicated by the problem that her i.v. cannulae sites rapidly became red and pustulous after insertion, despite careful skin preparation. A microbiological opinion suggested a likely primary immunodeficiency with impaired phagocytic function secondary to poorly controlled diabetes. The options for anaesthetic management of the planned procedures were discussed. In view of the patient's medical history and active hiatus hernia, a regional technique was preferred to general anaesthesia However, in view of the microbiological problems, insertion of an indwelling extradural catheter left for a period of days was discounted because of the probably low but real risk of extradural abscess formation. Also, over a 12-day period it was likely that at least two extradurals would have to be sited.

Thus intrathecal anaesthesia was the option chosen as the patient was apyrexial and receiving antibiotics.[3 4] The patient had 12 further intrathecal anaesthetics performed over a 19-day period, 10 performed on consecutive days. The patient suffered no post-puncture headaches, backache or other neurological sequelae. CSF was obtained at the last dural puncture which had a leucocyte count of 1 and was negative for bacteria. She was happy with her management, although expressed that she would have preferred an extradural technique for pain relief after operation.

Repeated diagnostic lumbar punctures have been described in paediatric cases suspected of meningitis,[5] but a patient having so many intrathecal anaesthetics over such a short time period has not. It may be an option in those patients in whom the risk of extradural abscess formation with an indwelling catheter is increased.

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British Journal of Anaesthesia 1998; **80**: 568–571

BOOK REVIEWS

Clinical Problems in Obstetric Anaesthesia I. F. Russel and G. Lyons (editors). Published by Chapman and Hall Medical, London. Pp. 292; indexed; illustrated.

In the forward to this book, Professor Philip Bromage describes the text as a "scholarly collection of contemporary essays". There are 20 in all, based on a common theme of identifying risks and using physiological and pharmacological principles of management to avoid or minimize them. These are the same factors governing training for the FRCA. With the majority of authors chosen from the UK, this book is welcome and reflects a developing need for obstetric anaesthetic textbooks to highlight European practice.

The emergency nature of obstetric anaesthesia is described in chapters on major haemorrhage, pre-eclampsia, antepartum emergencies, resuscitation, problems of intubation, emergency general anaesthesia, failure of nerve block and, not forgetting the two or more "consumers" of the process of obstetric anaesthesia, anaesthesia for the compromised fetus. It is this grouping of these essential clinical areas of obstetric anaesthetic practice which makes the book basic reading for all clinicians working full time, on an occasional basis or perhaps only "on call" in emergency obstetric anaesthesia. Added to this is the background of the contributors; all but one are from Europe and of those working in the UK, all but one are from north of Leicester. I am sure that this geographical selection does not imply that the incidence of this group of obstetric anaesthetic emergencies is more prevalent in these areas, but rather that it gives a clinically relevant and firm basis for the topics chosen.

Chapter headings are selected at random in this review which may give the reader a chance to explore the contents in more detail. For example, what problems may be associated with general anaesthesia for a woman who requires Caesarean section? Her risks from mortality (particularly airway difficulties and aspiration) are described in one chapter, her antenatal assessment (of the airway, including Mallampati score and communication of risk assessment) and her consent (with risk assessment) in separate chapters. The implications of physiological changes in pregnancy for the anaesthetist are reviewed briefly in the chapter on peripartum anaesthesia. Problems with tracheal intubation (using the pharyngeal soft tissue scoring of Samsoon and Young) and emergency anaesthesia with mortality and airway management are described in another two chapters. In vain, I searched for risks during the recovery period after general anaesthesia when there has been mortality, and where advice on safe monitoring would be useful. Pain relief after Caesarean section and the choice of antiemetics for a woman who has to be mobile and breast feed an infant would also be useful additions. However, there was plenty of information throughout the book on induction of anaesthesia and its risks, some of which are not well presented in general anaesthetic textbooks.

It was surprising, given the clinical expertise of one of the editors, Dr Ian Russell, that spinal anaesthesia and the problems associated with it were not part of a separate chapter Perhaps this was deliberate. If an anaesthetist is interested in this aspect of spinal anaesthesia, the failure rate of the combined spinal–extradural technique is presented, as is the use of spinal anaesthesia in pre-eclampsia. Maternal hypotension of 30–50% is quoted as a major disadvantage yet daily in clinical practice the use of spinal anaesthesia is increasingly being taught and practised. The problem of hypotension is discussed in the section on the compromised fetus. Management of peripartum fluid balance is not indexed but is mentioned briefly in the pre-eclampsia section, despite a chapter on acute (the terminology of "adult" is used in the book) respiratory distress syndrome. The prevention and management of hypotension associated with spinal anaesthesia is probably the most significant area missing from what is otherwise a rich source of clinical risks.

Other chapter topics are worth reading (rather than waiting in expectation for a woman to present with the condition). These include first, a comprehensive section on haematological disorders, both congenital and acquired; second, a section on cardiac disease containing a detailed, well referenced description of myocardial ischaemia in pregnancy; third, a wide ranging section on immune system functions written by an anaesthetist and extending to practical aspects of immunodeficiency syndromes; and fourth, drug abuse in pregnancy reflecting the expertise of Dr David Birnbach in New York and Dr A. Van Zundert from Eindhoven in the Netherlands.

The remaining chapters cover topics relating to morbidity. "The febrile obstetric patient" concentrates on extradural abscess and meningitis. Postpartum neurological disorders are considered separately. This section is potentially very useful because it identifies all of the peripheral nerve lesions (including cranial nerves), and the general lack of knowledge of the neuropathies which can complicate pregnancy itself is stressed. Co-existing neurological disorders are grouped in another chapter and begin with the commonest disorder, convulsions.

Finally, there are two chapters on the topical problems of backache and post-dural puncture headache. They are clearly written by the same authors, Drs G. Capogna and D. Celleno from Italy, and are appropriately illustrated. Adequate guidance is given for those obstetric anaesthetists who are developing guidelines for the prevention and management of post-dural puncture headache and backache, both distressing conditions for a mother after delivery.

The index appears to be very comprehensive. The system of page identification by the title of the chapter on one page and the individual page contents on the other enables quick reference to topics. One page, however, generated lateral thinking: it was titled "stable disorders". The text is easy to read, the line diagrams are clear and local guidelines are included where necessary from hospitals within Europe. It is clearly a book to have available on the labour ward for ease of reference. However, the editors, Drs Ian Russell and Gordon Lyons, have also made a substantial contribution to the teaching of safe obstetric anaesthetic care.

A. Holdcroft

International Anesthesiology Clinics (Mechanical Ventilation), vol. 33. B. Deb and R. G. Pearl. Published by Lippincott–Raven, Hagerstown, Maryland. Pp. 182; indexed; illustrated.

This small book is in the *International Anesthesiology Clinics Series*, and perhaps because of that, has a strong north American bias, with unfortunately no European contributors. The preface contains little more than the list of contents, and I cannot be sure of the book's intended audience.

It starts with a chapter on the indications for mechanical ventilation, which I found particularly useful for its description of when mechanical ventilation is not indicated. This good start is followed by a dry description of conventional modes of mechanical ventilation, which includes little discussion. A chapter on weaning is curiously interposed between the foregoing and a chapter on non-invasive ventilation, but both are readable and informative. The chapter entitled "Monitoring mechanically ventilated patients" seems to describe complications more than monitoring, but that simply illustrates its commendable emphasis on clinical relevance. The chapter on ventilators in the operating room is heavily directed towards a few American ventilators, from Ohmeda and North American Drager, with little generality. In particular, the discussion of cross-infection (six lines) is inadequate. The book closes with four clinical chapters on the role of mechanical ventilation in acute respiratory distress syndrome, chronic obstructive airways disease, paediatric practice, and the place of ECMO, all of which include a sufficient number of references to recent work.

There are some obvious omissions in this volume. For instance, high frequency modes of ventilation are discussed briefly in the chapter on paediatrics, but the reader is referred to review articles and "other chapters" which I have been unable to identify.

So who is this book for? The chapters most relevant to anaesthetic training are the poorest, especially from a European perspective, so I cannot recommend the book to trainees in general. On the other hand, the chapters relating to intensive care, which are the majority, are excellent reviews for more senior trainees. I would not recommend individual purchases, but I think some use could be made of this book in an intensive care unit. I shall leave my review copy there.

G. G. Lockwood

Clinical Neuroanaesthesia. A. Schubert. Published by Butterworth-Heinemann, Massachusetts. Pp. 406; indexed; illustrated.

This enjoyable paperback comprises 23 chapters, each comprehensively referenced. The preface includes a contents index, organized by procedure; there is also a subject index at the end of the book. Divided into two parts, the first section of the book includes 15 chapters covering neuroanaesthesia for specific procedures. Later chapters (Nos 16–23) are devoted to concepts, complications and techniques. The text is written in American English aimed at the resident in anaesthesia, as a sub-specialty orientated manual, relevant to the working clinical anaesthetist in training who requires a text containing information pertinent to scheduled work for the next day.

This is a particularly readable book because clinical information is provided both from a broad literature base but also with opinions from the considerable experience of the author's clinical practice. In the first section the reader is familiarized with specific surgical procedures, and provided with relevant preoperative considerations, equipment and monitoring requirements, the conduct of the anaesthetic and clear goals to be aimed for during the procedure. Although an extremely practical reference manual for daily work, the comprehensive reference list at the end of each chapter provides a springboard for further in-depth study of the relevant subject.

The second section of the book covers basic physiological and pharmacological principles of neuroanaesthesia and deals with modern neuroanaesthetic monitoring techniques. Despite introduction of a more theoretical flavour into the text, explanatory data are integrated carefully into its relevant clinical context so that this section of the book retains clinical applicability. This is augmented by the author integrating examples to illustrate theoretical considerations from his own clinical practice.

I particularly enjoyed reading the last chapter of this textbook which deals with considerations during emergence from neurosurgical anaesthesia. This aspect of neuroanaesthesia is frequently not well covered in anaesthetic textbooks and the author has attempted to give the reader guidance over issues of delayed and abnormal emergence from neurosurgical anaesthesia. The practical flavour of the subject is illustrated by a simple scheme for evaluating patients slow to emerge from neuroanaesthesia that would be of considerable use to the neuroanaesthetist in training.

One irritating feature was the use of cross referencing in the subject index. Thus "vasospasm" is cross referenced to "see cerebral vasospasm" and "transcranial Doppler" is cross referenced to "see cerebral blood flow, transcranial Doppler for measurement of" without giving the page number at the original locus.

The reader should be aware that some clinical management advocated in this textbook has a pro-American style and would differ from current European practice. This is partly reflected in a predominance of American literature cited at the end of each chapter. For example the stance taken by the author on the use of steroids in spinal cord injury would be different to that adopted in much of Europe. Where there are discrepancies between American and European practice these issues are not debated. With this reservation, I would strongly recommend this small book both as a practical manual for the neuroanaesthetist in training and as a source of useful reference material for greater depth of study of aspects of clinical neuroanaesthesia.

N. M. Dearden

Pain in the Elderly. B. R. Ferrell and B. A. Ferrell (editors). Published by IASP, Seattle, Washington. Pp. 137; indexed; illustrated. Price $25.00.

This short book consists of a collection of 11 reviews covering topics pertinent to pain in the elderly. It represents the result of the appointment of a task force on pain in the elderly by the International Association for the Study of Pain.

The first contribution provides a brief overview of the process of ageing and the disease processes associated with it. This, of course, is an enormous subject and the chapter does not attempt to describe in great detail any aspects of this area. However, it is a useful simple summary.

The second chapter describes pain in its cognitive–behavioural perspective. It is a good, standard description of this topic, with specific comments relevant to the elderly where appropriate. There follows an excellent review of the pharmacology of opioids and other analgesic drugs with respect to the elderly. This contribution has several useful tables and is a fine review of the pharmacological literature. There are real pharmacological differences between the young and elderly and the authors have highlighted these well.

The next chapter describes various non-drug interventions and educational techniques which are appropriate for the elderly patient. In essence, it is a description of the author's approach to the management of elderly cancer patients and their families. It is a very personal review but embraces many basic principles and is a useful starting point for those with no experience in the area. A later chapter considers cancer pain in the elderly also and to some extent there is crossover with previous chapters. This is inevitable but again it is well written with many useful pointers.

The field of postoperative pain management in the elderly is reviewed—another difficult task. However, in general, the authors have succeeded in crystallizing the important points. I would certainly recommend that any health care professional involved in the management of postoperative pain in the elderly patient should read this chapter. The next chapter aims to address the problem of chronic non-malignant pain in elderly people. This is another enormous topic but the authors have managed to summarize very many studies quite succinctly. There follows a brief dissertation on the multidisciplinary management of chronic non-malignant pain in the elderly Again, this is a precise and useful description of this difficult area.

The final chapters cover the management of pain in the elderly at home and the issues surrounding family involvement, high technology strategies, social support, etc. Although these chapters are well written, they are quite specific to the North American situation. Finally, there is an attempt to view the problem from an international perspective, but this is an almost impossible task and falls well short of the mark.

In summary, this is a very useful volume which I feel is essential reading for any practitioner involved in the management of pain in the elderly. The only disappointment is that there has been very little attempt to make it a truly international piece of work. The vast majority of the material is written by North American practitioners and there is little reference to the situation in the rest of the world. I was disappointed with this as one would have expected the International Association for the Study of Pain to attempt to enrol a wider and more representative panel of authors. Despite this, it is still a useful contribution to the literature and comes highly recommended by this reviewer.

D. J. Rowbotham

PK-SIM: The Pharmacokinetic Simulator, v. 3.11. R. H. Epstein. Published by Specialized Data System, Jenkintown, Pennsylvania. Price $99.95.

This computer program is intended to allow pharmacokinetic simulations for i.v. anaesthetic drugs, and to show the effect of changes in dose regimen or in pharmacokinetic variables on the plasma concentration profile. It is designed to be a teaching aid, and to allow students to perform "what if" experiments. It provides for simulation of concentrations in the effect compartment, and allows simultaneous display not only of plasma and effect site concentrations, but also drug infusion rate, total drug dose or drug cost. The dose regimen is not restricted to single bolus doses, but allows multiple doses and changes in infusion rate; the program also deals with CACI regimens which can be targeted on either plasma or effect site concentration.

The program runs under Windows 3.1 or Windows 95, and it was tested in both environments; first on an Intel 486DX based PC running at 33 MHz, and second on an Intel Pentium running at 120 MHz. A manual of 83 pages is provided.

A program such as this will be assessed both for its content and usability. It is notoriously difficult to write software which is easy to use, but the usability of this program will be judged against the very high standards of user-friendliness of other, quite different products currently available from major software development corporations.

The usability of this product left much to be desired. The originally distributed disks failed to install correctly owing to omission of a necessary library file, which was supplied rapidly by the author. Thereafter, the program installed correctly, and this defect will surely be fixed in subsequent releases. On starting the program, one enters a main screen with a toolbar; running a simulation results in the formation of a simulation window. The sizing of the windows was an impediment to easy use; the main screen failed to maximize fully, and in the Windows 95 environment it was not possible to fit the whole of the simulation screen into the window. This criticism also applies in both environments to other windows, for example the pharmacokinetic parameter database window and the infusion protocol window; the user is therefore required to do much scrolling which should be unnecessary.

There are other respects in which this product does not feel quite "finished". There is a parameter conversion window which allows conversion of a set of pharmacokinetic parameters to an alternative parameterization. This allows incompatible sets of parameters to be entered, and while there is a general warning both on the screen and in the manual, it would seem better to disallow behaviour such as the presentation of negative half-lives more explicitly.

The help screens are disappointingly brief and lack a searchable index or hyper-links. There are some unnecessary frills: the option to view three-dimensional charts together with user specified rotation of the charts must add programming complexity to little purpose.

Good points of the program include the rapid execution of simulations; for example a 4-h infusion running on an Intel 486 based PC at 33 MHz can be calculated in only a few seconds.

The content includes a series of tutorials to illustrate a series of pharmacokinetic concepts, including the idea of drug redistribution, the effect site, target based infusions, and context sensitive half-lives. The tutorials each occupy 1–3 pages of the manual, and the relevant simulations can be loaded from a drop-down menu. The tutorials are the best feature of the program; for example lesson 4 demonstrates why a loading dose of propofol is needed—this is basic and simple, and it makes the point.

The smooth flow of the tutorials is interrupted by discrepancies (usually a numerical difference) between the manual and the loaded simulation. There are some errors also: lesson 5 concerns the effect site, and the manual describes the rate constant *k*eo (without units) as a number between 0 and 1.

The program models effect site concentrations, but it does not deal directly with effect. Thus it models temporal aspects of effect, in particular the lag between plasma concentration and effect, but not with the magnitude of response that might be expected from a dose regimen. A meaningful prediction of effect will, of course, not always be possible, but where it is (and this includes the neuromuscular blocking agents), it would enhance the simulations considerably.

The final two lessons are on inter-individual variability and comparative pharmacokinetics. The user is invited to experiment by altering parameters, but the usefulness of the program as a teaching aid would be enhanced by provision of more specific examples, for which the necessary information is available Additional tutorials on the effect of age, obesity and renal failure on plasma concentration profiles would be useful.

In summary, this program is only partially successful. Some students might learn valuable lessons from it, but it needs further attention to usability, and expansion of the tutorials.

C. J. R. Parker

Acute and Chronic Pain. International Anesthesiology Clinics, vol. 35, No. 2. A. R. Molloy and I. Power (editors). Published by Lippincott-Raven, Philadelphia. Pp. 213; indexed; illustrated.

This is a very useful small book, written and edited by the staff at the Royal North Shore Hospital, Sydney. Michael Cousins' imprint is clear, although sadly the first two references in his preface are transposed! Despite the book's title, the main emphasis is on acute and perioperative pain, with only three chapters on chronic pain. The book is designed to provide an update for those already involved in pain management, and to "stimulate anesthesiologists to consider the field of pain management as a future professional activity".

Each chapter gives a succinct up-to-date review of its topic. The first chapter sets the scene well with a useful review of pain physiology. The book then focuses on advances in acute pain management, followed by a discussion of new opioid analgesics. There is an interesting chapter dealing with neuropathic pain in the perioperative period, suggesting that acute, intensive intervention may avoid or significantly reduce the development of central neurobiological changes and subsequent chronic pain—a tenet based on experimental pain in animals. This is not well supported by the referenced clinical studies. Acute pain and the obstetric patient focuses on ropivacaine and the combined spinal–extradural technique, although the analgesic properties of intrathecal neostigmine are mentioned. Acute pain management in paediatric patients is discussed succinctly. I was surprised that the discussion of non-steroidal anti-inflammatory drugs did not mention the problem of Reye's syndrome. This may not be a new problem, but surely it should not be forgotten.

The next three chapters cover chronic pain, and discuss neural block in chronic and cancer pain, cognitive–behavioural programmes and neuraxial implants. This suggests that information is scant, but taken alongside the excellent discussions of drug treatment for acute neuropathic pain, and the chapter on opioids, the book provides useful guidance to present concepts. But the use of drugs in the long term and for chronic pain is not delineated. The final chapter discusses the education of postgraduates, and the diploma that is provided at the Royal North Shore Hospital.

In general, this is a very readable, well written book of concise reviews, spoiled only by the shortcomings I have mentioned.

T. P. Nash

Problems in Anaesthesia—Controversies in Neuroanaesthesia, vol. 9, No. 1. D. S. Prough and M. H. Zornow (editors). Published by Lippincott-Raven, Philadelphia. Pp. 141; indexed; illustrated.

As the title suggests, this book contains a series of reviews on topical subjects in the field of neuroanaesthesia. This monograph is part of a series entitled "*Problems in Anesthesia*". It is the first edition of the new series restarted after a 2-yr break. If the aim of the book was to discuss controversies in neuroanaesthesia, it has failed because there is little controversy; however, if the aim was to provide useful updates on topical areas of interest to neuroanaesthetists with discussion of those areas which may be controversial, the authors have succeeded. The clinical chapters have a significant bias towards North American practice as almost all of the authors are from North America, with the only European being from Vienna.

At the beginning of the book there are short summaries of individual chapters which accurately reflect their content. The chapters include a thorough review of the place of nitric oxide in the control of the cerebral circulation which addresses its possible neurotoxic and neuroprotective effects. This is followed by a well written and easily understood summary of the current concepts of the mechanisms by which anaesthetics provide neuroprotection. This links well with a later chapter on the management of cerebral arterial occlusion during endovascular treatment of cerebrovascular disease, in which the clinical use of agents with cerebral protective effects is discussed. The topics discussed in the other chapters are airway management of patients with cervical spine injury, blood substitutes, haemoglobin-based solutions and perfluorocarbons, with their potential applications in neurosurgery, perioperative management of head injury, role of hypothermia in clinical practice, perioperative management of aneurysmal subarachnoid haemorrhage, brain monitoring in neurosurgery, venous air embolism and regional anaesthesia for carotid endarterectomy.

There are a few errors, which include an incorrect description of the Hagen–Poiseuille law, an inaccurate description of the physical principles of near infrared spectroscopy and inclusion of hypoxia and anaemia as causes of decreased cerebral blood flow. The description of P wave changes during the introduction of a central venous cannula does not give details of the ECG lead and connection used. Without this information, discussion of the changes in direction of the P wave is meaningless. These errors mean that the book cannot be recommended to trainees preparing for examinations. However, the reviews are of high quality and I would recommend the book to neuroanaesthetists as an update which should make a significant contribution to their continuing medical education. This book would be a useful addition to the shelves of libraries in hospitals with a neurosurgical unit.

E. Moss

International Anesthesiology Clinics. Airway Management in Pediatric Anesthesia, vol. 35, No. 3. L. M. Borland (editor). Published by Lippincott-Raven, Philadelphia. Pp. 177; indexed; illustrated.

This issue of *International Anesthesiology Clinics* includes a range of topics presented at the Third International Symposium on the Pediatric Airway in Orlando, Florida, November 1996. There are 15 chapters covering imaging of the airway to various problems associated with airway obstruction. The editor and all but three of the 16 authors are from the Children's Hospital of Pittsburgh, Pennsylvania, so that the book could be said to be from a single institution and perhaps reflects the philosophy of that institution. This is exemplified by the two chapters on laryngotracheal reconstruction by Barbara Brandom and colleagues who review the literature and then present the management and results of their studies in patients in Pittsburgh. In these and other chapters they emphasize the role of gastro-oesophageal reflux in the aetiology, and its effect on the subsequent management of patients with subglottic stenosis.

It is not surprising with a multi-author book that the style of each chapter varies considerably. For example, the chapter on advanced airway management by prehospital personnel is a discourse on the advantages and disadvantages of the use of sedatives and neuromuscular blocking agents before intubation by paramedics, and includes an algorithm for their use. In contrast, that on the role of gastric juice and peptide growth factors in subglottic stenosis is a scientific paper of the authors' work, with methods, results and discussion sections. It is a prerequisite that any book on airway management has a section on the laryngeal mask airway, and this chapter has plenty of useful information, including Benumof's algorithm for the difficult airway.

In an era of evidence-based medicine, how does this book fare? There is alot of evidence presented of the opinions of the authors and each chapter has extensive reference sections. But there are examples of confused presentation and evidence is contradicted. For example, in the chapter on sinusitis and lower airway reactivity, the authors state that there is no scientific evidence that decongestants are effective for the treatment of sinusitis in children; they go on to say that in their experience decongestants are effective. I was unsure if this is experience over evidence or that the evidence does not exist. Although there are several illustrations within the text, some in the chapter on x-ray imaging are of poor quality. The chapter on airway complications of HIV infection could have benefited from some photographs of the diseases mentioned.

As the chapters are not too long, ranging from 4 to 18 pages, they were relatively easy and quick to read; this is a book in which to dip in and out. On the whole, the book was informative and will be of use to anaesthetists with an interest in the paediatric airway. But this is by no means a complete reference book on the management of the difficult paediatric airway.

A. R. Bowhay

Self Assessment Colour Review of Cardiothoracic Critical Care. R. C. Karmy-Jones and H. Mathilda Horst (editors). Published by Manson Publishing, London. Pp. 176; indexed; illustrated.

This is a collection of 262 questions, with accompanying answers, from 26 contributors, predominantly working in Detroit, USA. The format is pocket-sized (15×20 cm). There are three or four questions on each page with their accompanying answers overleaf. The majority of questions are illustrated with good reproductions of x-rays, ECG, CT scans, line diagrams and occasional colour prints.

Analysis of the type of questions reveals that approximately 20% are intensive care topics; 20% basic pharmacology and physiology; 20% general surgical management; 10% emergency room management of trauma; 10% ECG analysis and cardiology; 8% paediatrics; and the remainder a miscellaneous collection, predominantly on cardiac surgery and cardiac anaesthesia.

The two editors describe the aims of this book as providing: a self-assessment review for those preparing for certifying examinations; a reference for common and uncommon problems; and a teaching tool for those involved in teaching junior medical professionals and medical students. In general, I believe the editors have achieved their aims The style and content are excellent for those preparing for examinations and for revealing those areas where additional revision is necessary. Similarly, this provides a bank of topics and examples which can be used in teaching. However, as is inevitable with a book of this size, it cannot be considered a source of reference, particularly as none of the answers has further reading suggestions.

The editors have thoughtfully provided a glossary to explain 163 abbreviations, but unfortunately this is not exhaustive. I found repeated referral to the glossary irritating and at times was left wondering why abbreviations had been used. This is a minor criticism. Although the content was more heterogeneous than I was anticipating from the book's title, I found the text generally interesting and stimulating. Because of the size and style of the book, I would expect it to be carried around and dipped into during the odd minutes that occur during any working day. I believe this book should find its way into most departmental libraries and it would also be a useful purchase for those preparing for examinations.

M. A. Fox

British Journal of Anaesthesia 1998; **80**: 572

ERRATA

British Journal of Anaesthesia 1998; **80**: 77-84

p. 82. In the Conclusion, paragraph one, line seven, should read "Prevention of systemic hypoxaemia, hypotension and *hyperthermia* . . ." and not "hypothermia" as published.

British Journal of Anaesthesia 1998; **80**: 20-25

p. 20. In the section entitled "PEROPERATIVE MANAGEMENT", the doses of fentanyl are reversed. The correct version should read "Group E patients received fentanyl *15* μg ml^{-1}; group L patients received fentanyl *50* μg ml^{-1}".

"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL I

Is amnesia for intraoperative events good enough?

On recovery from a general anaesthetic, approximately 3 in 1000 patients recollect some aspect of intraoperative events.[1] This recollection indicates a deviation from "clinically adequate anaesthesia", for example, faulty anaesthetic technique or equipment failure.[2] It is often assumed that the converse is also true, that failure to recollect surgery indicates lack of awareness throughout surgery. That this is not the case is illustrated by the fact that patients can be aware during surgery or sedation yet remember nothing on recovery. For example, using the isolated forearm technique, Russell[3] showed that 11 of 25 patients (44%) receiving balanced anaesthesia responded appropriately to commands to squeeze their fingers, yet only one recalled intraoperative events on recovery. Schultetus and colleagues[4] similarly observed appropriate responses to command in 46% of women undergoing Caesarean section with thiopental or a combination of thiopental and ketamine. Only 13% (three patients) had postoperative recall of their intraoperative awareness.

We conducted a volunteer study with a similar outcome: participants receiving an end-tidal isoflurane concentration of 0.4% were able to respond (by raising their right thumb) to examples of a target category in lists of items from various categories, yet on recovery were unable to recognize the previously presented examples.[5] The article by Ghoneim, Block and Dhanaraj in this issue of the journal[6] replicates the previous demonstrations of responsiveness with no subsequent explicit memory. They administered isoflurane and midazolam to volunteers in doses that permitted occasional responses to commands to squeeze the researcher's fingers. Volunteers were read lists of words while receiving isoflurane (0.2% end-tidal concentration) and midazolam 0.03 mg kg^{-1} or 0.06 mg kg^{-1} i.v., yet on recovery could not identify those words with above-chance accuracy on a forced-choice recognition test. However, five of the 28 volunteers recalled at least one word presented during administration of the drug combination. Although for the purposes of statistical analysis this recall is negligible, in a clinical setting it might be cause for concern if 18% of patients recalled stimuli presented during anaesthesia. This aside, the finding of responsiveness with no subsequent explicit memory raises the question of whether or not some degree of awareness during surgery is acceptable providing patients are amnesic on recovery, or should awareness be prevented by increasing anaesthetic doses, despite the costs of increased side effects and prolonged recovery times?

The first issue is whether there is some implicit memory for stimuli presented during anaesthesia, even if there is no explicit memory. There have been many demonstrations of implicit memory being preserved by factors such as divided attention or subliminal presentation that reduce or abolish explicit memory,[7] and therefore perhaps anaesthetics also abolish explicit memory but preserve implicit memory. If this were the case, there might be cause for concern. Implicit memory, by definition, changes behaviour and lingering implicit memory for surgery might result in problems such as depression, insomnia, reluctance to return to hospital for follow-up treatment, etc. However, the results of volunteer studies suggest that anaesthetics tend to abolish explicit and implicit memory equally unless the stimuli are very simple (e.g. single words) and the dose of anaesthetic is very low, typically preserving speech and response to command.[8] In our own research, volunteers had neither implicit nor explicit memory for names presented during infusion of propofol in doses that not only preserved response to command but also allowed them to identify repeated items on a short-term memory test.[8] Therefore, it appears that all memory formation ceases at lighter anaesthesia (i.e. lower doses) than is needed for loss of response. The article by Ghoneim, Block and Dhanaraj[6] strengthens this conclusion. Volunteers in their study showed no priming by words presented during midazolam and isoflurane administration, even though they occasionally responded to commands during that period (unfortunately they do not report the incidence of memory specifically for words presented during moments of responding).

There are two reasons why we cannot confidently extrapolate from volunteer studies that no learning occurs in episodes of awareness during general anaesthesia for surgery: first, there is the paradox that clinical studies have demonstrated implicit memory for intraoperative events and second, tests such as word stem completion may not be very sensitive to the type of learning that may occur during surgery.

MacRae, Thorp and Millar report in this issue of the journal[9] that paralysed patients failed to learn words presented during anaesthesia, even when presentation followed a particularly stimulating procedure, such as intubation or first incision. There are many other reports of null results in this area, but also an approximately equal number of studies in which patients apparently learned stimuli presented during anaesthesia.[10] A possible explanation of this discrepancy is that the studies varied in depth of anaesthesia used, with learning occurring only when patients were lightly anaesthetized. Many researchers have assumed that implicit memory tests measure implicit learning, that is learning without awareness. The error of this argument is demonstrated by the many observations of preserved implicit memory in amnesics whose learning, but unfortunately not their memory, is explicit.[7] Implicit memory may result from implicit or explicit learning, therefore implicit memory for intraoperative stimuli reveals nothing about awareness during surgery. Did patients have implicit memory because they were aware of the stimuli presented during surgery? This remains a possibility in the absence of some objective information on depth of anaesthesia during their operations,[11, 12] but learning during clinical anaesthesia may also occur because of physiological changes induced by surgery,[13] or it may be an artefact resulting from poor methodology.[8, 10, 14]

Implicit memory tests such as the word stem completion task used by Ghoneim, Block and Dhanaraj[6] and the category generation task used by MacRae, Thorp and Millar[9] assess what Murphy and Zajonc[15] refer to as "cognitive priming". Zajonc[16] has argued that affective, or emotional, priming can be elicited with much less cognitive mediation. Murphy and Zajonc[15] demonstrated this using a task in which participants were asked to guess the meanings of Chinese ideographs and rate them on a scale of 1 ("represents a bad object") to 5 ("represents a good object"). Extremely brief (4 ms) presentations of angry or happy faces primed participants' ratings of the ideographs, happy faces being associated with higher ratings than angry faces. Interestingly, longer presentations (1 s) of the faces had no effect on the good/bad ideograph ratings. The subliminal presentations only primed the emotional (good/bad) judgements and not ratings on a scale of small to large. Affective priming, measured as changes in emotional responses, may be triggered by emotive stimuli presented at depths of anaesthesia sufficient to obliterate cognitive processing. Such affective priming, coupled with lack of explicit memory for the emotive stimuli themselves, may result in a state of free-floating anxiety.[15] It is not known if affective priming occurs during surgery with general anaesthesia, although anecdotal reports, such as that of the woman who became depressed after allegedly hearing the surgeon exclaim "She is fat, isn't she?",[17] suggest that it may occur.

We conclude that patients may be responsive during sedation or anaesthesia yet have neither implicit nor explicit memory for events occurring during that time. If awareness has so little impact on memory, then amnesia *per se* may be good enough, providing patients can come to terms with the prospect of being conscious during surgery even though they will be amnesic on recovery. However, it should be remembered that Russell,[18] using the isolated forearm technique, asked 20 patients receiving midazolam, alfentanil and a neuromuscular blocking agent to indicate if they were in pain. All 20 patients were aware and experienced pain at some point during surgery, but none recalled the pain or other intraoperative events when questioned in the recovery room. We suspect that the possibility of being aware and in pain during surgery might be alarming and unacceptable for many patients. Russell[18] did not report if the experience of pain during surgery was associated with any adverse emotional changes on recovery. However, the anecdotal evidence mentioned above, and the research by Zajonc and colleagues on affective priming, suggest that the emotional impact of awareness during anaesthesia needs to be considered. If future research shows that abnormal emotional reactions only occur after surgery with light anaesthesia, then the benefits of increasing the dose of anaesthetic (and potential side effects and recovery times) should be evaluated. If, however, such reactions occur regardless of depth of anaesthesia, then alternative solutions, for example increasing intraoperative analgesia or perioperative reassurance, should be investigated. Amnesia may not be good enough but it may be the best we can achieve without further research.

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EDITORIAL II

Orphanin FQ/nociceptin: an endogenous peptide agonist for the orphan opioid receptor

Cloning of the opioid receptor family has added a new dimension to opioid pharmacology. In common with the endogenous μ δ κ opioid subtypes, recombinant opioid receptors, when expressed in a variety of cell types, couple to K^+ channels, Ca^{2+} channels and adenylyl cyclase.[1–4] The net effect in the CNS is reduction in neuronal firing and excitability. If this occurs in neurones involved in the processing of noxious stimuli then analgesia results. Despite these monumental advances the clinical "holy grail" of analgesia without respiratory depression remains to be realized. In this editorial we summarize briefly a new development in opioid pharmacology—isolation of a novel receptor involved in pain processing and discovery of an endogenous ligand for this receptor.

Shortly after the publication of the μ δ and κ opioid receptor sequences several groups reported the isolation of an atypical "opioid-like" receptor subtype[5–11] with approximately 50% homology to μ δ and κ opioid receptors. There is general consensus that these different clones represent the same receptor. From sequence and structural analysis the receptor is predicted to be a new member of the G-protein coupled receptor superfamily and is known euphemistically as the orphan opioid receptor (ORL_1). A common characteristic of the orphan receptor was that opioid receptor ligands bound with very low affinity compared with opioid receptors. In the rat, orphan receptors are found "scattered" throughout the CNS with high levels found in the thalamus, hypothalamus, amygdala, cortex (diffuse but layered), hippocampus, periaqueductal gray, dorsal raphe, locus coeruleus and spinal cord.[5–11] At the time of cloning no endogenous ligand had been isolated.

In November 1995, Reinscheid and colleagues[12] and Meunier and colleagues[13] reported the isolation of a heptadecapeptide (fig. 1) that was named orphanin FQ or nociceptin (throughout the remainder of this editorial orphanin FQ (OFQ) is used and refers to the full 17 amino acid peptide). The heptadecapeptide displayed nanomolar binding affinity for the recombinant ORL_1 receptor in radioligand binding studies. The first amino acid differed in OFQ compared with opioid peptides, but of these peptides its closest match was with dynorphin (fig. 1). When injected intracerebroventricularly (i.c.v.) (i.e. supraspinally) in the mouse, the peptide appeared to be hyperalgesic.[12 13] In addition, it has been reported recently that OFQ is a functional opioid antagonist. OFQ was shown to completely block supraspinal antinociception in mice mediated by selective μ δ and κ agonists.[14 15] Stanfa and colleagues reported that OFQ inhibited C-fibre-evoked wind-up and post-discharge of dorsal horn neurones,[16] concluding that OFQ was antinociceptive at the spinal level. These differences at spinal and supraspinal sites clearly need further exploration. Unlike μ receptor activation orphan receptor activation with OFQ (and hence a clinical orphan receptor agonist when available) does not produce dependence and as such has little or no abuse potential.[17]

The cellular effects of OFQ have received some attention and have been shown to inhibit cAMP formation.[12 13] In addition, OFQ increases inwardly rectifying K^+ currents[18–20] and inhibits voltage-sensitive Ca^{2+} channels.[21 22] Activation of K^+ channels, closing of voltage-sensitive Ca^{2+} channels and inhibition of adenylyl cyclase are features common to opioid receptors.[1–4] We have demonstrated recently that OFQ inhibits the release of glutamate from rat cerebrocortical slices in a naloxone-insensitive manner.[23] These data are in agreement with the inhibitory effects of OFQ on glutamatergic transmission in the rat spinal cord.[24] If this depression in glutamatergic transmission is mirrored in the hippocampus then this might provide an explanation for the effects of OFQ on spatial learning.[25] Similarly, if observed in the cerebellum, this may go some way to explain the effects of OFQ on locomotion.[12 25] In addition to glutamate, OFQ also inhibits the release of tachykinin,[26] acetylcholine[27 28] and dopamine.[29] These data suggest the presence of presynaptic ORL_1 receptors involved in neurotransmitter release. Is OFQ released in significant quantities to provide inhibition of release under physiological conditions? This is another important issue that needs to be resolved in the near future. The recent development of a sensitive radioimmunoassay[30] should prove useful in this regard.

1. Orphanin FQ/Nociceptin

Amino acid sequence

Phe-Gly-Gly-Phe-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln

Single letter code

Orphanin FQ

FGGFTGARKSARKLANQ

2. Dynorphin

Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln

3. Met-enkephalin

Tyr-Gly-Gly-Phe-Met

4 β-endorphin

Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Val-Lys-Asn-Ala-His-Lys-Lys-Gly-Gly

Figure 1 Amino acid sequence and single letter code of the heptadecapeptide nociceptin/orphanin FQ. Amino acid sequences of dynorphin met-enkephalin and β-endorphin are included for comparison. Amino acid code· Ala=alanine; Arg=arginine, Asn=asparagine, Asp=aspartate, Cys=cysteine, Gln=glutamine; Glu=glutamate, Gly=glycine; His=histidine; Ile=isoleucine; Leu=leucine; Lys=lysine; Met=methionine, Phe=phenylalanine; Pro=proline; Ser=serine; Thr=threonine, Trp=tryptophan; Tyr=tyrosine; Val=valine.

The clinical significance of OFQ has yet to be fully explored but studies reporting hyperalgesia (although these have been questioned) raise some interesting clinical questions. For example, in pain states will there be increased concentrations of OFQ spinally or supraspinally, or both? Are there any clinical applications for OFQ antagonists? Where should OFQ or an antagonist be administered? Spinally, OFQ may be expected to produce analgesia[16] but spread to supraspinal sites via spinal or i.v. administration may produce hyperalgesia[12 13] or even reverse opioid-mediated analgesia.[14 15] Conversely, administration of antagonist at spinal sites may reduce analgesia whereas access to supraspinal sites in chronic pain states may facilitate the actions of opioids. These suppositions need to be explored in a coordinated manner using the skills of medicinal chemistry to design an OFQ antagonist, basic pharmacology to assess its potential, and clinicians in pain specialties to evaluate its clinical potential.

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EDITORIAL III

Stature of anaesthetic personnel and positioning of patients

Anaesthetists and their assistants come in many shapes and sizes. Administering anaesthesia (and assisting the process) involves physical skills in the performance of several techniques. Can there be a connection between these two statements? It is many years now since a friendly colleague, observing my i.v. cannulation technique, suggested that either I needed longer arms or spectacles. Devices to combat presbyopia are easily acquired, socially acceptable and no one thinks twice about using them. Are there other clinical situations where we should consider simple methods of compensation for physical diversity? With the certainty of being politically incorrect, I shall refer to vertically challenged and those of below average height as short. I think we should pay some attention to the difficulties encountered by short people who become part of the anaesthetic team.

In this issue of the journal Meek, Vincent and Duggan[1] describe the difficulty of maintaining cricoid pressure for more than a short time in the simulated circumstances of induction of anaesthesia. If times for laryngoscopy and intubation are prolonged, protection from regurgitation may be interrupted. They showed that it is easier if the assistant's arm can be extended and the elbow locked. A first thought might be that a very tall assistant is a good idea; a second thought might be to lower the trolley. Currently, the latter is often impossible. The ability to place the patient's head down is a generally accepted prerequisite for induction of anaesthesia and it should be possible to bring the head and neck low enough for easy application of cricoid pressure. However, it may encourage regurgitation. In addition, it may leave the anaesthetist, already in difficulties, coping with a patient in an even more difficult position. We have all performed intubations on our knees, but few favour it. A simpler answer is to use the platform(s) provided in operating suites for members of the team. Each adds 12 cm and they are designed to fit securely if more than one is used.

Stature-related difficulties also attend resuscitation. A small study indicated that those shorter than 176 cm were unlikely to be able to maintain external cardiac compression for as long as 1 min when tested on a mannikin placed on a standard operating table at its lowest position (84 cm).[2] In recent years, it has seemed more difficult to teach laryngoscopic technique to novices, and although the increased prevalence of anterior tooth restorations and obesity (in patients) undoubtedly contribute, there may be other factors.[3] Patient trolleys seem to be higher than when I started training (88 cm is common); they certainly have thicker mattresses (70–80 mm *vs* 30 mm). These changes probably result from concern for nurses' backs and patient comfort.

Although some of the recent changes in anaesthetic training have been less than enthusiastically received, detailing more of the requirements is generally regarded as helpful. The brief learning materials issued by the Royal College of Anaesthetists instruct trainees to "Learn how to teach your anaesthetic assistant to apply cricoid pressure". A recent editorial emphasized the vocational nature of medical education and outlined the increase in competency-based training.[4] It did not comment on the fact that training of anaesthetists' assistants is now based on the level 3 National Standard for Operating Department Practice within the National Council for Vocational Qualifications scheme.[5] Perhaps all anaesthetists, rather than a self-selected few, should take an interest in the system that provides them with such a general level of excellent help. Application of cricoid pressure is dealt with under element (a) of unit 6: "Assist at establishing the patient's airway". Second among the performance criteria is "The patient is appropriately positioned for establishing the airway". Within the "range" statement under procedures rapid sequence induction and cricoid pressure are listed.

All that seems to be required therefore is that trainers and assessors of anaesthetists and their assistants should maintain best practice within these frameworks. Precisely what they should teach however is not absolutely clear and I refer later to some areas of difficulty. They would be aided by further simple research into the effectiveness of the technique of application of cricoid pressure under a range of circumstances and of the teaching of the technique.

Our day-stay unit has been equipped with trolleys that function as operating tables thus eliminating the need for patient transfer. I regarded this initially as extravagant but soon realized that the capacity to adjust the height of the patient—nice and high for cannulation to save my back, a bit lower for airway management, even lower for short trainees—was ergonomically attractive. I believe we have some evidence to justify additional costs. We are assessing possible replacements for our theatre trolleys. The sophistication of design available in comparison with our current stock is striking. Two of the models proffered are easily adjustable for height giving a range of mattress surfaces of approximately 70–97 cm. These trolleys will give the anaesthetist and assistant more control of their circumstances and are preferable to positioning the patient on the operating table before induction (a manoeuvre that can cause considerable pain and distress). Platforms must still be available for extreme conditions.

There is a need for anaesthetists to focus on these simple physical matters. Surgeons are accustomed to having the patient placed in the most appropriate position for their surgical procedure. No ENT surgeon would start a laryngoscopy without having the patient's head as near to the top of the operating table as possible and the angles of the head, neck and shoulders as they perceive correct. Our airway manipulations are just as important and may be time dependant for patient safety; our techniques need to be at least as rigorous. We should not start induction of anaesthesia without considering if the position of the patient is optimal. We may judge that causing pain by moving them is not justified in a case where no difficulty is anticipated but this should be a conscious judgement. All too often valuable time is lost by having to adjust pillows when the patient's airway is unsecured. Textbooks stress correct positioning for airway management[6] but it is an index of our failure to emphasize the importance of this to medical students during their anaesthetic attachment that junior doctors faced with the perceived need to intubate in the absence of an anaesthetist almost universally remove the patient's pillows.[7] Welcoming the patient to the anaesthetic room and identifying oneself as their anaesthetist (now dressed differently) should be followed by explicit attention to position. Moving the pillow(s) from under the shoulders has the added bonus of a grateful "Ah that's better" from many patients.

Many failed intubation drills commence with a laudable preamble about checking the anaesthetic machine suction equipment etc. I have not found one (including our own!) that mentions the patient's position *before* induction of anaesthesia, although Harmer[8] suggests repositioning pillows when difficulty is experienced in inserting the laryngoscope. However an extra anomaly emerges with regard to cricoid pressure. There is apparent conflict between the requirement for flexion of the neck to produce good conditions for laryngoscopy and extension of the neck to provide effective cricoid pressure.[9] Even my personal favourite when it comes to a clear description of laryngoscopic technique, the *Synopsis of Anaesthesia*,[10] having prescribed neck flexion subsequently details the application of cricoid pressure: "the neck is extended..". It may be useful to regard the neck as a rigid column when explaining laryngoscopy but it becomes an oversimplification with reference to application of cricoid pressure: flexion and extension are not adequate as single descriptors of cervical spine posture. Authors who refer to necessary neck flexion[11] as "lower" neck flexion help to resolve this difficulty as it seems likely that the flexion caused by unopposed cricoid pressure and referred to as increasing laryngoscopic difficulty[8] occurs higher up the cervical spine. Trainers and trainees deserve a clearer exposition of what should be taught.

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CLINICAL INVESTIGATIONS

Interaction of a subanaesthetic concentration of isoflurane with midazolam: effects on responsiveness, learning and memory

M. M. GHONEIM, R. I. BLOCK AND V. J. DHANARAJ

Summary

There are situations in which "light" anaesthesia combined with neuromuscular block is the only anaesthetic regimen that can be tolerated safely by the patient. Benzodiazepines have hypnotic and specific amnesic effects. Therefore, we have examined the interaction of midazolam with a subanaesthetic dose of isoflurane (0.2% end-expired concentration) in 28 healthy volunteers. Thereafter, 15 subjects received midazolam 0.03 mg kg^{-1} i.v. and 13 subjects received midazolam 0.06 mg kg^{-1} in a random, double-blind manner. Word lists were administered and response to commands was tested before and after administration of midazolam. After 1 h of recovery, memory for word lists was tested by word completion, free recall and forced choice recognition tasks. After administration of midazolam, recall and, to a lesser degree, implicit memory were absent. Recognition was also absent after administration of midazolam 0.06 mg kg^{-1} and at the 3-min and 15-min assessments after administration of midazolam 0.03 mg kg^{-1}. Responsiveness was more frequent with midazolam 0.03 mg kg^{-1} than with 0.06 mg kg^{-1} and increased over time. We conclude that a larger dose of midazolam or isoflurane, or both, may be necessary to abolish responsiveness. (*Br. J. Anaesth.* 1998; **80**: 581–587)

Keywords. anaesthetics volatile isoflurane; hypnotics benzodiazepine midazolam; memory; anaesthesia depth

There are common anaesthetic and surgical situations in which "light" anaesthesia combined with neuromuscular block may be the only anaesthetic regimen that can be tolerated safely by the patient (e.g. obstetrics, emergence from cardiopulmonary bypass, trauma surgery and patients with debilitating physical diseases). Anaesthetists are unable to determine reliably whether or not a given anaesthetized, paralysed patient is conscious during surgery. Clinical physical signs during anaesthesia are not helpful and there is no monitor that can detect awareness. Regaining consciousness during surgery and recalling this experience after operation can be a devastating experience.[1] Benzodiazepines have hypnotic and specific amnesic effects.[2] Their effects on the cardiovascular system are relatively mild compared with other anaesthetics and the severity of a patient's cardiac disease does not appear to significantly influence haemodynamic responses.[3] Therefore, it may be advisable to use a benzodiazepine whenever "light" anaesthesia is necessary, to avoid awareness and recall. There is synergism between benzodiazepines and volatile anaesthetics when used in combination.[4 5] This interaction could be beneficial in reducing the required dose of benzodiazepine.

The aim of this study was to examine the interaction of two doses of midazolam with a typical subanaesthetic dose of isoflurane on responsiveness, learning and memory.

A distinction of memory, of particular interest to anaesthesia, is between explicit and implicit memory. Explicit memory refers to intentional or conscious recollection of prior experiences, as assessed by tests of recall or recognition. In contrast, implicit memory refers to changes in performance or behaviour that are produced by prior experiences on tests that do not require any intentional or conscious recollection of those experiences.[6] The basic distinction between explicit and implicit tests involves the nature of the instructions given to the subjects. In an explicit test, subjects are asked to recall or recognize events that have been presented before. In an implicit test, the instructions make no reference to these earlier events. We assessed explicit memory by using free recall and recognition tasks and implicit memory using a word completion task. The latter task has become the prototypical task in research on priming, that is hearing or seeing the words on the list increases the likelihood of subjects responding with these words in the subsequent word completion test. This test has been used frequently to demonstrate preserved performance of amnesic patients[7 8] and in drug research on memory, including anaesthetics.[9]

Subjects and methods

We studied 28 healthy subjects. Subjects were excluded if they were suffering from any illness, were pregnant or were receiving medications, particularly centrally active agents; if they had used three or more illicit drugs; or if they were heavy users of alcohol or marijuana. Female volunteers were screened for pregnancy before the sessions. The study was approved by the local Institutional Review Board.

EXPERIMENTAL DESIGN

All subjects inhaled 0.2% end-expired concentration of isoflurane for 15 min to ensure equilibration with

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Table 1 Schedule for the study

Time (min)	Procedure
−20	Signing the consent form and instructions
−16	Administration of 0.2% end-expired isoflurane concentration
−1	Response to command task and presentation of one word list
00	Administration of midazolam
+2	Response to command task which was repeated every 2 min thereafter
+3	Presentation of one word list. Subsequent word lists were administered at 15, 30 and 45 min
+46	Administration of the last response to command task, followed by cessation of isoflurane administration
+47	Break for recovery
+107	Word completion test, followed by delayed free recall test and then recognition test

arterial blood and brain partial pressures (table 1). Thereafter, 15 subjects received midazolam 0.03 mg kg^{-1} (Versed) i.v. and 13 received midazolam 0.06 mg kg^{-1} in a random, double-blind manner. The subject and research technician administering the tests were blinded to the dose of drug administered. The word lists (see below) were counterbalanced in the order in which they were presented. Control groups of volunteers who would have received isoflurane alone and midazolam alone were not included because data are already available on their effects on responsiveness and memory.[10–14]

EXPERIMENTAL SESSIONS

Subjects were tested individually while lying on a reclining hospital stretcher. Isoflurane was administered via a mouth-piece attached to a semi-closed anaesthetic breathing system. A nose-clip prevented contamination of the inspired gases with room air. An end-tidal concentration of 0.2% isoflurane, as measured by mass spectroscopy, was maintained for 15 min. Arterial oxygen saturation, carbon dioxide concentration in expired air and heart rate were also monitored. *Response to command* and *memory list presentation* were then administered as a baseline assessment ("isoflurane baseline"). Thereafter, one of the two doses of midazolam was given i.v. over a 2-min period. Response to command was tested every 2 min for 46 min after administration of midazolam. Different word lists were administered at 3, 15, 30 and 45 min after administration of midazolam. Inhalation of isoflurane was stopped after testing the last response to command and, after one additional hour of rest, memory for the word lists was tested.

TASKS

Response to command

At each assessment, ability to comprehend language and make a voluntary motor response to a verbal command was assessed by asking the subject to squeeze the research assistant's fingers. Instructions to squeeze two or three times were given in random order. In all analyses of responsiveness, appropriate responses were contrasted with "unresponsiveness," which was defined as either a lack of response or an inappropriate response (the latter were rare, constituting only 5% of all "unresponsiveness").

Memory assessments

(1) Learning stage. We prepared six lists of words, each consisting of eight words. The words were selected from those used in a previous study.[14] The lists were equated on Thorndike–Lorge word frequency and normative free recall.[15–17] None of the words on these lists had the same initial three letters. For each word on the lists, at least 10 common words in the English language began with the same three letters.

The words on the lists were presented auditorily and visually simultaneously at a rate of one word every 5 s. For each subject, five of the six lists were used for one presentation before and four presentations after administration of midazolam. The remaining list was not presented. Words on this list served as "distracters" on the implicit memory test, that is a control condition, as described below. The assignment of specific lists to the different times of presentation and distracter condition were approximately counterbalanced over subjects receiving each dose of midazolam, using a Latin square design.

(2) Memory test stage. After 1 h of recovery from the effects of isoflurane and midazolam, implicit memory was tested by a word completion task. The subject was given a page containing the first three letters (e.g. "con", "pen", "man") of the 48 words on all six lists (e.g. "concern", "pension", "manual"), including the "distracters" on the list that was not presented. The words from all lists were mixed together in random order. For each three-letter word beginning, the subject was asked to write the first word that came to mind beginning with those letters. The relationship between this test and the previous presentations of lists of words was not explained. The lists were equated on spontaneous frequencies of giving the words as responses to the word beginnings, based on our earlier results.[14] The numbers of list words that were supplied by a subject on the word completion task were counted for each memory list presentation; to calculate the "priming" score (measure of implicit memory), these numbers were reduced by the number of words supplied by the subject on the word completion task for the control words that were not presented to him. Thus a priming score of zero reflected the absence of implicit memory, while a positive priming score reflected the presence of implicit memory.

After completing the word completion task, recall was tested. The subject was instructed to write the words from all previously presented lists. This was followed by a forced choice recognition test in which subjects had to choose which word had been presented previously for each of a series of word pairs.

STATISTICAL ANALYSIS

Recognition and priming scores were submitted to repeated measures analyses of variance, with

Table 2 Subject characteristics (mean (SD or range) or number)

	Midazolam 0.03 mg kg^{-1}	Midazolam 0.06 mg kg^{-1}
Sex (% men)	60.0	46.2
Age (yr)	22.2 (19–32)	22.2 (19–31)
Education (yr)	15.1 (0.4)	14.3 (0.3)
Weight (kg)	68.5 (2.6)	68.4 (3.4)
Height (cm)	171.3 (2.3)	174.9 (2.7)
Body mass index (kg cm^{-2})	0.002 (0.0001)	0.002 (0.0001)

midazolam dose (0.03 mg kg^{-1} *vs* 0.06 mg kg^{-1}) as a between-subjects factor and test condition (the control condition defined above, the isoflurane baseline after isoflurane but before midazolam administration, and 3, 15, 30 and 45 min after administration of midazolam) as a repeated measures factor. When appropriate, Huynh-Feldt adjusted probability values[18] were used. Pre-planned Helmert contrasts[18] were performed to compare the control condition *vs* all other conditions, baseline *vs* all conditions after midazolam, and each condition after midazolam with all conditions after midazolam subsequent to it. Corresponding analyses were neither necessary nor feasible for recall, as discussed below.

To examine if the memory test scores presumably reflecting implicit and explicit memory processes were independent, Pearson correlations of priming (reflecting implicit memory) with recall and recognition (reflecting explicit memory) were computed for the midazolam 0.03 mg kg^{-1} and 0.06 mg kg^{-1} groups for each word list presentation.

Appropriate responses to command were examined with respect to dose and three time intervals after administration of midazolam bounded by the word list presentations at 15 and 30 min after midazolam. A model based on a first-order Markov process[18] was used to relate responsiveness at each individual time of assessment within these intervals (i.e. 2–14, 16–30, and 32–46 min, after administration of midazolam) to responsiveness at the immediately preceding time. This model resulted in a 2×3×2×2 contingency table that was subjected to hierarchical log-linear analysis to test how responsiveness at each individual time was influenced by dose, time interval and responsiveness at the immediately preceding time.

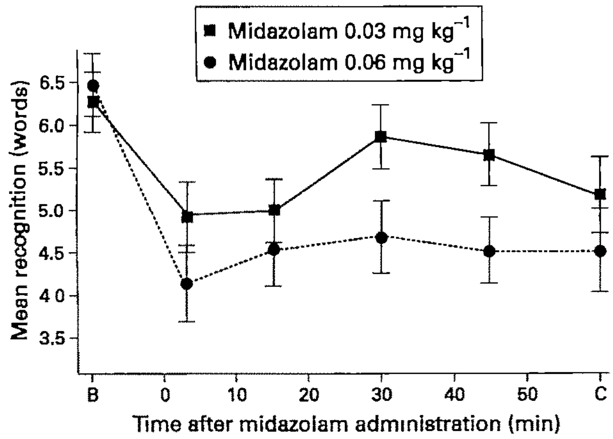

Figure 1 Mean (SEM) recognition scores (numbers of words recognized) for words presented at the isoflurane baseline (B), at the four memory list presentations after administration of midazolam, and words that were not presented (control (C)). Eight words were presented at each memory list presentation. The control scores, also based on eight words, were calculated separately for midazolam 0.03 mg kg^{-1} and 0.06 mg kg and reflect chance levels of performance.

Because some subjects seemed to drift in and out of whatever degree of consciousness was necessary to respond appropriately to commands, "fluctuations" in responsiveness, defined as occasions on which one or more consecutive appropriate responses were both preceded and followed by unresponsiveness, were compared for the midazolam 0.03 mg kg^{-1} and 0.06 mg kg^{-1} groups by a *t* test. Pearson correlations were also computed between the number of fluctuations and free recall, priming and recognition averaged over all four word list presentations after administration of midazolam.

To determine if there was implicit memory for words presented while subjects were unresponsive, priming scores were analysed for the earliest list presentation to each subject after administration of midazolam which was both immediately preceded and immediately followed by unresponsiveness. Priming scores in the midazolam 0.03 mg kg^{-1} and 0.06 mg kg^{-1} groups were compared with each other and to the chance score (zero) by *t* tests. Only 16 subjects (six who received midazolam 0.03 mg kg^{-1} and 10 who received midazolam 0.06 mg kg^{-1}) were included in these analyses, because no list presentation met the criterion for the remaining subjects.

The initial durations of unresponsive periods after administration of midazolam 0.03 mg kg^{-1} and 0.06 mg kg^{-1} were compared by life table analysis.[19] Similar analysis methods were also applied to the maximal durations (i.e. the longest continuous sequences) of unresponsiveness and their times of onset.

All analyses were performed using the statistical computer package SAS v.6.

Results

Patient characteristics in the midazolam 0.03 mg kg^{-1} and 0.06 mg kg^{-1} groups did not differ significantly in sex distribution, mean age, years of education, weight, height or body mass index (table 2).

RECALL

At the isoflurane baseline, recall did not differ significantly between the midazolam 0.03 mg kg^{-1} and 0.06 mg kg^{-1} groups (mean 2.1 (SEM 0.5) words and 2.5 (0.4) words, respectively). After administration of midazolam, recall was virtually absent to a degree that made statistical analysis unnecessary. Only one subject (in the midazolam 0.03 mg kg^{-1} group) recalled any words at 15 min after administration of midazolam and four subjects (three from the midazolam 0.03 mg kg^{-1} group and one from the midazolam 0.06 mg kg^{-1} group) recalled words at 45 min after administration of midazolam. No subject recalled any words at either 3 min or 30 min after administration of midazolam.

RECOGNITION

Recognition scores are shown in figure 1. The repeated measures ANOVA showed significant effects of dose ($F(1, 26)=9.84$; $P=0.0042$) and time ($F(5, 130)=4.65$; $P=0.0006$), although the global dose×time interaction was not significant ($F<1$). The

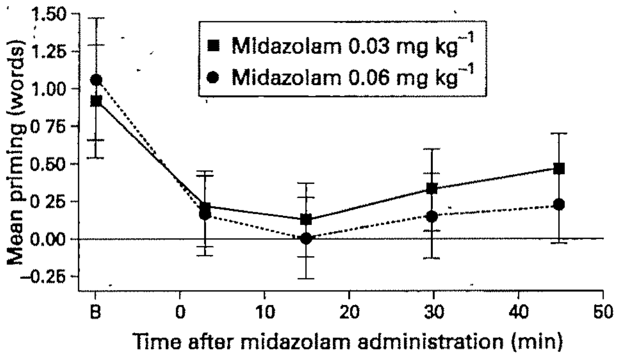

Figure 2 Mean (SEM) priming scores (reflecting implicit memory) in the word completion task for words presented at the isoflurane baseline (B) and the four memory list presentations after administration of midazolam. Data are included for all subjects, without regard to response to command. The number of words supplied by subjects on the implicit memory test for the control words that were not presented to them and which were subtracted in calculating the priming scores (see text) were, mean 0.6 (SEM 0.2) words for midazolam 0.03 mg kg^{-1} and 0.5 (0.2) words for midazolam 0.06 mg kg^{-1} The horizontal line at zero represents chance performance.

pre-planned Helmert contrast comparing isoflurane baselines with the means of all times after midazolam indicated that midazolam 0.06 mg kg^{-1} impaired recognition significantly more than midazolam 0.03 mg kg^{-1}. At the isoflurane baseline, recognition scores significantly exceeded chance level (i.e. performance on the control list); recognition scores in the midazolam 0.03 mg kg^{-1} and 0.06 mg kg^{-1} groups did not differ. Recognition was absent at all assessments after administration of midazolam 0.06 mg kg^{-1} and at the 3-min and 15-min assessments after administration of midazolam 0.03 mg kg^{-1}, that is recognition scores did not differ significantly from chance levels and remained below the levels of isoflurane baseline. However, as indicated in figure 1, there was some suggestion of recovery in performance at 30 min and 45 min after administration of midazolam 0.03 mg kg^{-1}; scores at these times, while still not different from chance levels, also did not differ from isoflurane baseline values.

PRIMING

Priming scores (reflecting implicit memory) in the word completion task for all subjects, whether or not they responded to command, are shown in figure 2. The repeated measures analysis of variance showed a significant effect of time ($F(4,104) = 4.13$, Huynh-Feldt adjusted $P=0.0069$), with the Helmert contrasts indicating that the effect was attributable to the decrease from isoflurane baseline to the four assessments after midazolam. Midazolam doses of 0.03 mg kg^{-1} and 0.06 mg kg^{-1} did not differ in their effects on priming; the effects of dose and dose×time were not significant. At the isoflurane baseline, priming significantly exceeded chance level (i.e. zero); priming scores for the midazolam 0.03 mg kg^{-1} and 0.06 mg kg^{-1} groups did not differ. Priming was absent after administration of midazolam, that is priming scores did not differ significantly from chance level (zero) and remained below the level at the isoflurane baseline.

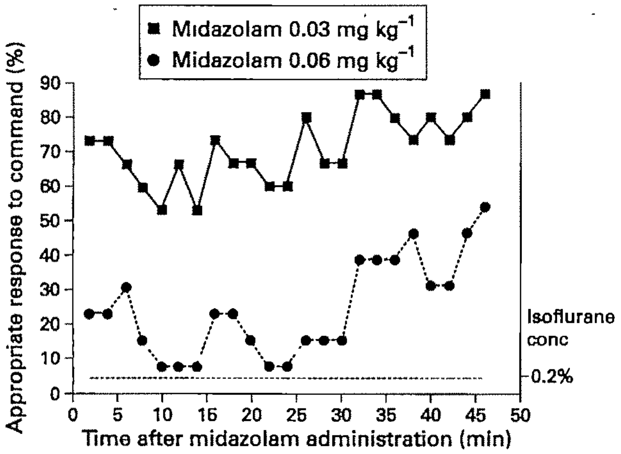

Figure 3 Percentages of subjects showing appropriate responses to command every 2 min for 46 min after administration of midazolam. The dotted line at the bottom illustrates the constant isoflurane concentration throughout this time.

CORRELATIONS OF IMPLICIT AND EXPLICIT MEMORY

Pearson correlations of priming (reflecting implicit memory) with recall and recognition (reflecting explicit memory) were not significant at the isoflurane baseline word list presentation or at any of the word list presentations after administration of midazolam in the 0.03 mg kg^{-1} group. Only one of the 10 correlations was significant for the midazolam 0.06 mg kg^{-1} group, that is between priming and recognition at the isoflurane baseline ($r=0.69$, $P=0.0086$).

RESPONSIVENESS

The percentages of appropriate responses to command are plotted for each 2-min time interval after midazolam in figure 3 and for the time periods involved in the first-order Markov process in figure 4. The model that resulted from the hierarchical log-linear analysis indicated that appropriate responsiveness was independently influenced by dose, time period and responsiveness at the immediately preceding time ($P<0.0001$, $P=0.0017$ and $P<0.0001$, respectively). Responsiveness was more frequent with midazolam 0.03 mg kg^{-1} than with 0.06 mg kg^{-1}, and increased over time. The association between current and immediately preceding responsiveness indicated that, in general, when subjects were responsive they tended to remain responsive, and when they were unresponsive they tended to remain unresponsive.

INITIAL AND MAXIMAL DURATIONS OF UNRESPONSIVE PERIODS

Life table analysis indicated that initial durations of unresponsive periods were longer with midazolam 0.06 mg kg^{-1} than with 0.03 mg kg^{-1} ($P=0.0024$, Wilcoxon test). Median durations were 30 min and 0 min, respectively. However, even midazolam 0.06 mg kg^{-1} did not produce immediate, prolonged unresponsiveness in 25% of subjects; 25% of subjects responded appropriately at 2 min or 4 min after administration of midazolam.

Maximal durations of unresponsive periods were longer with midazolam 0.06 mg kg^{-1} than with 0.03 mg kg^{-1} ($P=0.0017$, Wilcoxon test). Median durations were 32 min and 4 min, respectively. Furthermore, the times of onset of unresponsive periods of

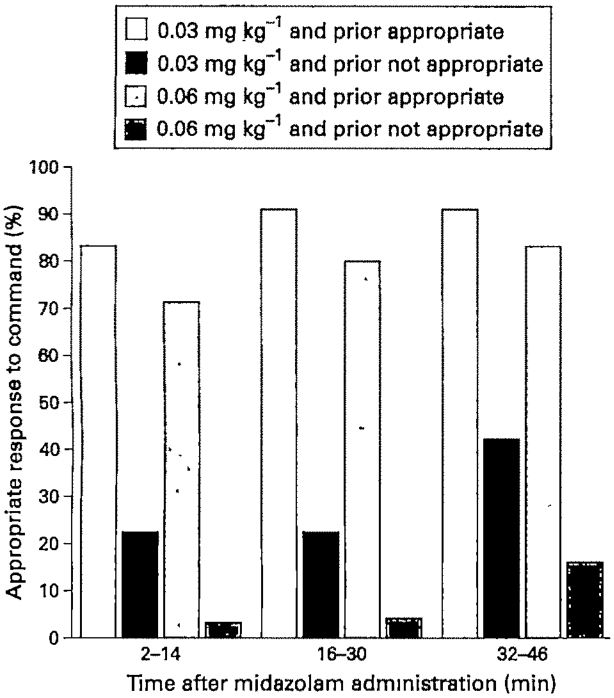

Figure 4 Percentages of subjects showing appropriate responses to command for the three time intervals (2–14 min, 16–30 min and 32–46 min after administration of midazolam) used in the model based on a first-order Markov process. As described in the text, the Markov process modelled the transition probabilities associated with the four possible combinations of responsiveness and unresponsiveness at each pair of successive times. The two types of bars designated in the legend as "prior appropriate" indicate the percentages of appropriate responses to command, given that the immediately preceding assessment showed an appropriate response to command. The other two types of bars, designated in the legend as "prior not appropriate," indicate the percentages of appropriate responses to command, given that the immediately preceding assessment did not show an appropriate response to command.

maximal duration also differed between midazolam 0.06 mg kg^{-1} and 0.03 mg kg^{-1} (P=0.0479, Wilcoxon test); the medians were 2 min and 10 min, respectively.

IMPLICIT MEMORY DURING UNRESPONSIVE PERIODS

Analysis of priming scores (reflecting implicit memory) during the earliest word list presentation to each subject after midazolam which was both immediately preceded and immediately followed by unresponsiveness provided no evidence of implicit memory. The priming scores in the midazolam 0.03 mg kg^{-1} and 0.06 mg kg^{-1} groups were -0.33 (0.42) words and 0.20 (0.25) words, respectively. These scores did not differ from chance level (zero) or from each other.

FLUCTUATIONS IN RESPONSIVENESS AND THEIR RELATIONSHIP TO MEMORY

Because some subjects seemed to drift in and out of whatever degree of consciousness was necessary to respond appropriately to commands, fluctuations in responsiveness (as defined above) were examined. The number of such fluctuations per subject did not differ significantly between the midazolam 0.03 mg kg^{-1} and 0.06 mg kg^{-1} groups (1.1 (0.3) and 0.8 (0.3), respectively). As presentation of word lists may have had an arousing effect, we also examined transitions from unresponsiveness to responsiveness and vice versa, excluding the times at which lists were presented. These analyses also showed no significant differences between midazolam 0.03 mg kg^{-1} and 0.06 mg kg^{-1} (1.1 (0.3) and 0.6 (0.3), respectively, for transitions from unresponsiveness to responsiveness; and 1.1 (0.3) and 0.8 (0.3) for transitions from responsiveness to unresponsiveness).

Pearson correlations were calculated to assess if memory was related to fluctuations in responsiveness. The correlation of fluctuations with recognition was significant for midazolam 0.03 mg kg^{-1} (r=0.56, P=0.0302), but not for midazolam 0.06 mg kg^{-1} (r=−0.22, P=0.48). The correlations of fluctuations with priming (reflecting implicit memory) and recall were not significant for either midazolam 0.03 mg kg^{-1} or 0.06 mg kg^{-1}.

Discussion

We evaluated responsiveness by ability of subjects to respond to verbal instructions by squeezing the research assistant's fingers two or three times. In the absence of other explanations for failure to respond to command, such as impaired hearing, hysteria, muscle paralysis and difficulty in differentiating between purposeful movement and reflex movements in response to surgical stimulation, such failure is currently the accepted indicator of the threshold between wakefulness or consciousness and unconsciousness.

The effects of midazolam and 0.2% isoflurane on responsiveness were somewhat variable. Four subjects (one who received 0.06 mg kg^{-1} and three who received 0.03 mg kg^{-1}) never lost consciousness. The other subjects lost responsiveness for variable periods of time. Responsiveness was more frequent with midazolam 0.03 mg kg^{-1} than with 0.06 mg kg^{-1} and increased over time. The times of onset of unresponsiveness were a function of the dose and were slower than the onset that has been reported after administration of larger doses used for induction of anaesthesia.[3] Some subjects seemed to drift in and out of consciousness and one subject remained responsive all of the time, only to lose consciousness during the last 15 min of the session. Midazolam is used for induction of anaesthesia and decreases the anaesthetic requirements (MAC) for volatile anaesthetics.[5] However, benzodiazepines, in clinical doses, do not reliably suppress processing of sensory and, especially, auditory stimuli.[20] When combined with opioids (e.g. alfentanil and midazolam)[21] most patients seem to be in an amnesic–analgesic plane, rather than truly unconscious.[22] Our data suggest that a larger dose than 0.06 mg kg^{-1} or a higher concentration of isoflurane, or both, are necessary to abolish responsiveness.

Both doses of midazolam, when added to 0.2% isoflurane, almost completely abolished both explicit and implicit memory. The impairments extended for most of the 45-min period after administration of midazolam. These results are in agreement with our previous study[14] which showed that midazolam impairs both types of memory. Demonstration of both explicit and implicit memory in addition to responsiveness in all subjects during administration of 0.2% isoflurane is in agreement with the studies of

Dwyer, Bennett and Eger[11] and Chortkoff, Bennett and Eger,[12] but different from the results of Newton and colleagues,[10] who found that during administration of 0.2 MAC of isoflurane, recall and recognition were lost.

The profundity of the effect of midazolam on recall was evident, as only one subject who received the 0.03 mg kg^{-1} dose recalled any words that were presented between 3 and 30 min after administration of the drug. Our conclusion that midazolam abolished implicit memory must be more tentative and tempered by consideration of the study's power to detect a small residual priming effect. Seven of the eight priming scores for words presented after midazolam administration were positive (fig. 2) and may have significantly exceeded chance level (zero) if more subjects had been tested. Calculations based on the variability of these scores indicate that mean priming scores of approximately 0.5–0.6 would have significantly exceeded chance level. The difference from chance level of the highest priming score observed for words presented after midazolam administration (0.47 score in the midazolam 0.03 mg kg^{-1} group for words presented at 45 min after midazolam administration) was marginally significant (P=0.07). None of the other priming scores for words presented after midazolam administration approached even this level, however.

An advantage of a control group would have been to allow separation of drug effects on memory from possible effects on memory of variations in the lag between presentation and testing of the word lists. For the lists presented after midazolam administration, this lag ranged from 1 h to 1 h 42 min. It is possible that the shorter lags for the lists presented 30–45 min after administration of midazolam 0.03 mg kg^{-1} compared with those presented earlier, could have contributed to the apparent recovery in recognition at these times. However, the finding that recognition was best for the list presented at the isoflurane baseline, which involved the longest lag between presentation and testing, suggests that changes in recognition were more related to recovery from midazolam than the passage of time.

Performance on implicit tests of memory are prone to influence by explicit memory if subjects become aware of the relationship between study and test items and exploit this knowledge.[23] All but one of the 20 correlations between implicit and explicit memory examined in this study (including all but one of the four correlations examined at the isoflurane baseline) were not significant, suggesting that this was not a problem.

We looked for implicit memory when subjects were unresponsive and examined the correlation of fluctuations in responsiveness with priming, a measure of implicit memory. There was no evidence of implicit memory in unconscious subjects and there was no significant correlation between the fluctuations in responsiveness and priming. Furthermore, there was no significant correlation between fluctuations in responsiveness and recall. This agrees with results of studies using the isolated forearm technique in which patients responded to commands without explicit recall.[22 24 25] Can episodes of intraoperative consciousness without subsequent recall, similar to the conditions of the present study, cause harm? There is no direct evidence for this possibility, but there are a few anecdotal reports[26 27] of unfavourable comments voiced during anaesthesia and retrieved under hypnosis that caused psychological disorders. Unfortunately, case reports cannot establish a cause and effect relationship, particularly where techniques such as hypnosis, which can sometimes lead to spurious recall, have been used.

In addition, there are two discrepancies between the conditions of our report and the clinical situation. The first is that our study involved only healthy volunteers who were not subjected to surgical stimuli. It is likely that greater doses would be required to suppress responses in the presence of more powerful stimuli than those used in our study. We elected not to administer painful stimuli (e.g. tetanic peripheral nerve stimulus or immersion of a forearm in ice-cold water) to our subjects to simulate the clinical situation for two reasons. The first was ethical and concerns inflicting painful stimuli on subjects who retain responsiveness and memory, particularly during inhalation of 0.2% isoflurane. The second was practical and concerns the problem of finding a sustained painful stimulus to represent surgical arousal.[13] The other discrepancy is that in some clinical situations, brain and blood concentrations of anaesthetics are not in equilibrium. A study such as ours would be difficult to conduct in patients during surgery for ethical reasons. Studying volunteers under controlled conditions provides more reliable data with assessments performed during a stable end-tidal concentration of inhaled anaesthetic after it has presumably reached equilibration with the anaesthetic partial pressure of the brain.

In summary, both doses of midazolam (0.03 and 0.06 mg kg^{-1}), when combined with 0.2% isoflurane in a quiescent environment devoid of surgical stimuli, almost completely abolished both explicit and implicit memory. Impairments extended over the 45-min period after administration of midazolam. However, the effect of the two drugs on responsiveness was more variable. Administration of midazolam to patients receiving only a subanaesthetic concentration of an inhalation anaesthetic is recommended to avoid recall. A larger dose than 0.06 mg kg^{-1} or a higher concentration of isoflurane than 0.2% may be necessary to abolish responsiveness.

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Category generation testing in the search for implicit memory during general anaesthesia

W. J. MacRae, J. M. Thorp and K. Millar

Summary

We gave auditory examples of two semantic categories through headphones to 100 surgical patients anaesthetized with propofol and enflurane. This presentation was made during certain stages of the procedure, potentially associated with arousal, and during steady-state anaesthesia. Postoperative review using category generation tests showed successful priming in a pre-induction group but no evidence of implicit memory in the anaesthetized groups. These results suggest that timing an auditory input to coincide with surgical stimulation does not increase the probability of retrieval of information by this type of testing. (*Br. J. Anaesth.* 1998; **80**: 588–593)

Keywords: anaesthetics volatile, enflurane; memory, implicit; anaesthesia, depth

Intraoperative awareness occurs if the intensity of the surgical stimulation is not matched by an appropriate level of anaesthesia. Alternatively, faulty anaesthetic technique or equipment may be responsible for an alert state and subsequent memory for the event. The sensitivity of testing of recall has been increased by the division of memory into explicit and implicit components.[1] Explicit memory is conscious recall of information and often of the events surrounding the original learning. In contrast, implicit memory involves the passive and unconscious activation of existing memory traces but without subsequent conscious memory of the initial activating incident. This process is also known as priming because it makes subsequent spontaneous recall of the activated memory more likely. The occurrence of implicit memory under surgical anaesthesia might imply an undesirable lightening of anaesthesia or, alternatively, it might be of therapeutic value.[2 3] In most studies, the terms implicit learning and implicit memory are conflated. If learning of auditory information occurs during a period of wakefulness of which the patient is subsequently amnesic, explicit learning with subsequent implicit memory may be said to have occurred. On the other hand, if learning of information has occurred while unconscious, both learning and memory were implicit.

Studies of implicit memory under anaesthesia have yielded both positive[4–8] and negative[9 10] results. The inconsistency of findings may be because the majority of studies have presented the information to patients throughout the surgical procedure. For those studies with positive results, it is not possible to establish whether priming was most effective at a given stage in the anaesthetic procedure. (A recent review of memory and learning[11] highlighted the need for further study to establish the salience of stimulating events in this respect.) It has been suggested[12] that there may be specific times during a surgical procedure when potential wakefulness can occur. If wakefulness is a prerequisite for the formation of implicit memory, it would be logical to examine the results of auditory stimuli presented at those particular times for evidence of differential effects.

An early study by Eisele, Weinreich and Bartle[13] attempted to show that recall after operation could be related to the time during operation when information was presented. In their study, patients were allocated randomly to one of five groups. The auditory stimulus was presented to each group at one of the following times: before induction, during operation, before extubation, in the recovery room or when fully awake after operation. Some patients, only from the intraoperative group, were monitored for galvanic skin response (GSR) as an indicator of arousal. In these patients, the stimulus was presented only when GSR indicated arousal. No evidence of intraoperative recall was shown despite GSR-indicated arousal. The groups who had heard the stimulus before operation or when fully recovered had complete recall, while the pre-extubation and recovery room groups had impaired recall. This particular study was criticized[14 15] for assessing only depth of anaesthesia in a minority of patients when information was being presented. Moreover, the sensitivity of memory tests has subsequently improved.

We have used category generation testing as a test of implicit memory, which has been shown previously to produce positive results during anaesthesia.[5 6] Also, we investigated if the occurrence of implicit memory varied as a function of the time during the procedure when the auditory information was presented. Steady-state anaesthesia was also compared with times of potential wakefulness, such as intubation, incision and recovery, when implicit memory might be established.

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This article is accompanied by Editorial I.

Patients and methods

We studied surgical patients undergoing elective or emergency procedures during general anaesthesia. The study was approved by the area Ethics Committee and all patients gave informed consent. Patients were aged 16–70 yr, ASA I–III. Exclusion criteria were hearing difficulties, history of psychotropic or benzodiazepine drug use, local anaesthetic use before skin incision and if English was not the first language. As enflurane was used for anaesthesia, patients with renal failure (acute or chronic) or a history of epilepsy were also excluded. Computer-generated random numbers allowed allocation to one of five groups for the timing of the auditory stimulus.

The category priming and generation task was adapted from Jelicic, Bonke and Appleboom.[5] The category generation task requires the subject to generate a list of exemplars of a named category as they come spontaneously to mind. When collated across a group of individuals, such lists often show remarkable similarity in the first three or four words generated (e.g. for "animals", most people immediately generate dog, cat, horse, sheep, etc, as being familiar exemplars). Other exemplars (e.g. tiger, camel), while still familiar, are less likely to be produced early in a generation sequence, if at all.

Prior exposure to category exemplars often results in a greater probability of their being generated in a generation task, and to their being among the first words and in a sequence, even when the subject has no conscious recall of prior exposure. Clearly, if priming is to be demonstrated, it is pointless to choose highly familiar target words which have a high probability of being generated even without priming. Relatively less familiar target words should be chosen so that if priming is effective, there is the potential for them to be generated more often and earlier in the generation sequence than would otherwise be the case.

A preliminary study in a similar surgical population of 50 patients allowed selection of three familiar examples of each of two semantic categories "fruit and colours". Examples of these categories were selected for the population in this area and were designated as *target words*. The words were selected by the investigators and had been produced by >50% of patients but did not commonly occur as one of the first three words generated (i.e. in serial positions one, two or three). The chosen examples of the two categories, fruit (peach, grape and melon) and colours (black, pink and purple), were recorded onto tape for use in the main study. This information was also used subsequently in the control group for comparison with the experimental groups. A further category "vegetables" was also generated, and these were used as *control words* in the postoperative testing.

The information was presented via a personal stereo set with headphones. The tape was recorded professionally with a male voice and the first part of the tape was an introduction for the investigator to check satisfactory function before placing the headphones on the patients for the 5-min recording. Each sequence of target words was preceded by the phrase "Please listen carefully to these words..." The control category, vegetables (onion, broccoli and cauliflower) was not presented to the patients during operation.

Patients were premedicated with pethidine and Phenergan (Pamergan) i.m., 60–90 min before operation. A standard anaesthetic consisted of an induction dose of propofol and maintenance with enflurane and 50–60% nitrous oxide in oxygen, with morphine for analgesia; neuromuscular block was not an exclusion criterion. The aim was to study adequate anaesthesia and this was based on clinical requirements rather than on a weight basis. The tape was played to each patient at one of the following times only: (1) pre-induction, (2) post-induction: immediately after intubation–placement of the laryngeal mask, (3) post-incision: immediately after the first incision, (4) steady state: 10 min after the first incision, and (5) recovery: enflurane administration discontinued and after breathing 100% oxygen for >2 min, with an end-tidal enflurane concentration of 0.1–0.3%. End-tidal enflurane concentrations were noted at the beginning and end of tape playing, after which the headphones were removed. The actual times of starting the cassette tape, cessation of anaesthesia and postoperative testing were recorded.

Category generation testing was carried out 5–24 h after the end of anaesthesia. Excluding 8 h for sleep, all patients were tested within 14 h of the auditory stimulus. The order in which patients free-associated to each category was randomized. Patients were asked to name examples (up to 10) of each category as they came to mind (including the control category which had not been presented during anaesthesia). The examples were written down by the interviewer and 2 min were allowed for each category. No mention was made of the taped information at this stage. Patients were subsequently asked to recall being in the anaesthetic room, their next memory after this (to assess explicit memory) and whether they had any recollection of information from the tape played during anaesthesia.

Data from category generation were analysed as follows. The hits score was the total number of target words generated. The serial position score took account of the position of a target in the list of generated words. The sequence rate defined those occasions where two or three targets were generated one after another. The null hypothesis was that there would be no difference either between the control and experimental groups or between the control category and target categories. Results were analysed with Minitab release 7.2, using two-tailed, non-parametric statistics, with adjustment for ties, where appropriate. Given the potential for multiple comparisons leading to type 1 errors, $P<0.01$ was set as the criterion for significance. To avoid type 2 errors, P values of 0.05–0.01 are reported.

Results

We studied 104 patients, of whom 100 completed the study; two patients refused to participate in the study and data were incomplete for two patients. There were no significant differences between groups in age, sex or period of time to testing. Comparisons were made of hits, serial positions and sequences of target word generation by the experimental groups and by the control group, and also between target and control words generated by the experimental groups.

Table 1 End-expiratory enflurane concentration (mean (SD)) during auditory stimulus and subsequent category generation, and serial position (median (interquartile range)) of successfully generated target words and control words

		Six target words		Three control words	
	Enflurane (%)	Hits (%)	Serial position	Hits (%)	Serial position
Control subjects (n=50)	0.0 (0.0)	64	6 (4–8)	51	6 (4–8)
Experimental groups					
Pre-induction (n=19)	0.0 (0.0)	84	4 (2–6)	53	5 (3–7)
Post-induction (n=21)	0.34 (0.3)	61	7 (5–8)	56	6 (4–7)
Post-incision (n=20)	1.05 (0.2)	70	6 (5–8)	58	6 (4–8)
Steady state (n=21)	0.92 (0.2)	60	6 (4–7.7)	48	6 (4–8)
Recovery (n=19)	0.28 (0.05)	56	6 (5–8)	63	5 (4–7)

HITS

There was a significant difference in hits between the groups (Kruskal–Wallis, P=0.001). The pre-induction group generated significantly more hits (table 1) than either the control group or any of the anaesthetized groups (Mann–Whitney, P<0.002 in each case), except for the post-incision group (P=0.03). When the pre-induction group was omitted from the former analysis, no significant inter-group difference remained. Within the anaesthetized groups, the post-incision group had the highest, and the recovery group the lowest, hit rate, but neither was significantly different from the control group. Comparing the groups for the control category (vegetables), there were no significant differences between groups (Kruskal–Wallis, P>0.7). The pre-induction group also showed a significantly higher hit rate for the target words than for the control words (Mann–Whitney, P=0.0009). No difference in hits between target and control words was found for any other group.

SERIAL POSITIONS

There was an overall difference between groups (Kruskal–Wallis, P<0.001) whereby the serial position of target words generated by the pre-induction group differed significantly from each of the experimental groups and from the control group (Mann–Whitney, P values all <0.0001) (table 1). Exclusion of the pre-induction group showed no significant difference between the remaining groups. For the pre-induction group, comparison of serial positions of target words and control words showed that although the target words were generated earlier, this was not significant (Mann–Whitney, P=0.015).

It was interesting that the recovery group, which had the lowest hit rate for the target words, also showed a lower median position for generated target words than for the control words, nearly achieving the set level of significance (Mann–Whitney, P=0.012).

It was postulated that if implicit memory were occurring, but only in a few patients, then a high hit rate might be associated with a higher median serial position. There was no evidence that this occurred; patients with five or six hits out of the possible six target words did not show any significant difference in serial position compared with similar high-scoring subjects in the control group, nor did they differ from the remainder of the experimental patients with fewer than five or six hits.

SEQUENCES

The pre-induction group generated significantly more sequences of target words than either the control group or any of the other experimental groups (Mann–Whitney, P<0.0001). There were no differences between the other groups (Kruskal–Wallis). The pre-induction group also showed significantly more sequences of target words than control words (Mann–Whitney, P<0.0001). For the control group and each of the anaesthetized groups, there was no difference between target words and control words (P>0.1).

It may be pertinent to view the sequences generated where sequence was a possibility; instances of one or no hit preclude this. In the pre-induction group, only one patient failed to generate at least two of the target words for colours while seven patients failed in this respect in the fruit category, but the

Table 2 Subjects giving two or three words in a sequence as a percentage of n; n=number of subjects in that group with two or three hits; N=total number of subjects in that group

	Target words						Control words		
	Colours			Fruit			Vegetables		
	n/N	2 (%)	3 (%)	n/N	2 (%)	3 (%)	n/N	2 (%)	3 (%)
Control subjects	42/50	35	5	31/50	32	3	26/50	35	4
Experimental groups									
Pre-induction	18/19	50	39	12/19	50	50	12/19	25	0
Post-induction	16/21	50	12	9/21	33	0	11/21	27	9
Post-incision	19/20	26	16	13/20	38	0	11/20	36	0
Steady state	16/21	44	12	10/21	30	0	12/21	42	0
Recovery	15/19	0	20	11/19	27	0	13/19	31	8

sequence rate was very high in the remaining majority (table 2). The recovery group, which had fewer hits and lower serial positions for target words, also had the fewest sequences of target words. As the hit rate for this group was lower, this might be anticipated. However, excluding instances of none or one hit, this group still demonstrated the fewest sequences for target words among the experimental groups. For the control words however, they were similar to the other groups in all respects. When instances of two or three hits were examined in the post-intubation group, a high sequence rate was noted for colours, with 50% of patients producing a sequence of two and a further 12% a sequence of three, but this was not statistically significant.

EXPLICIT MEMORY

No anaesthetized patient had conscious memory of the tape being played or of its content. No patient had recall of events between the anaesthetic room and the recovery area. After category generation, the pre-induction group was asked, as the final question, for explicit recall of the auditory stimulus. The 84% hit rate for the group was identical to that obtained for category generation, although for individual patients there were inconsistencies.

RECALL IN RELATION TO ANAESTHETIC STATE

In summary, there was no evidence of implicit memory in the anaesthetized groups. The lowest enflurane concentration during the 5 min of tape playing was in the recovery group (mean 0.28%) and the highest was in the post-incision group (mean 1.05 (SD 0.2)%) (table 1). For the nitrous oxide and enflurane components, these means were estimated to be equivalent to 0.2 and 1.2 MAC, respectively. This calculation excludes the effect of the other anaesthetic constituents. No correlation was found, or relationship seen, between generation of the target words and anaesthetic state or stimulating events. The presence or absence of neuromuscular block had no effect on target word generation or on the mean end-tidal enflurane concentration; the mean enflurane concentration was 0.1% higher in paralysed compared with non-paralysed patients. The pre-induction group performed significantly better than the control group and all experimental groups in respect of hits, serial position and occurrence of sequences. It was also significantly better in the generation of target words compared with control words. Despite the low enflurane concentration, as intended, the recovery group showed a tendency to be worse in all respects than the other groups; this was not significant.

Discussion

Our results do not provide evidence that implicit memory can be established through priming of verbal material during general anaesthesia. However, we used a method which provoked a priming effect in conscious patients (pre-induction group) hence indicating that the task itself had the potential to detect priming if it had occurred. The results are consistent with negative studies[9 10]; failure to support previous positive studies[4-7] may be explicable on one of several counts.

First, it could be that previous research made the methodological error of presenting stimuli throughout the procedure, hence increasing the chance of auditory stimuli occurring during unintentional light anaesthesia. Memory is expected to be absent for events from induction until surgery is completed, although approximately 0.5% of obstetric patients may have explicit memory of events where neuromuscular blocking agents are used during anaesthesia[16]; in non-obstetric anaesthesia this value may be nearer 1 in 3000.[17] In paralysed patients, stimulating procedures during the surgical event are associated with lightening of anaesthesia.[18 19] This study was designed to test the theory that implicit memory could be shown to occur at times when increased stimulation caused transitory arousal. Our method permitted examination of priming as a function of different stages of the surgical procedure, as did that of Eisele, Weinreich and Bartle.[13] Our result is consistent with Eisele, Weinreich and Bartle[13] but using a more advanced task and method. A later study, also using enflurane, showed a dose-related effect, with the early cortical components of auditory evoked responses (AER) being nearly abolished at an end-expiratory concentration of 1.22% enflurane in nitrous oxide.[20] In our study, the end-expired enflurane concentration during tape-playing was less than 1.2% in 95% of the fully anaesthetized patients.

MAC is more difficult to calculate with this type of anaesthetic, as nitrous oxide and enflurane end-tidal concentrations can be measured but the contributions of premedication, induction agent and intra-operative analgesia are ignored. Nor are their effects equivalent in all groups; premedication and induction agent would have minimal effects in the recovery group but substantial effects in the post-induction group. The rationale behind our study was that lightening of the anaesthetic state might occur at times of stimulation despite apparently adequate clinical anaesthesia and MAC values. In the absence of a gold standard for anaesthetic depth, vapour concentration or MAC may permit some comparison between positive and negative studies in anaesthetized patients. In volunteer experiments, with a simpler and more rigid anaesthetic procedure, Dwyer and colleagues[21] showed that the MAC-awake (the end-tidal concentration preventing voluntary response in 50% of subjects) for isoflurane was 0.38 times the MAC in healthy volunteers. Stress (i.e. surgical stimulation) may be expected to increase the concentration of isoflurane required to abolish implicit memory. In volunteers receiving 0.4% isoflurane, tetanic stimulation increased the coherent frequency and caused improved performance on memory tests, but these effects did not occur at 0.8% isoflurane.[22] Matter-of-fact information presented at concentrations just above MAC-awake has shown no evidence of implicit memory. However, emotionally charged information required a higher concentration of anaesthetic, although still less than the MAC value, to suppress memory.[23] Three of our four anaesthetized groups received the stimulus during stimulating events when arousal might occur.[18 19] Despite this, implicit recall could not be detected in these subjects.

A second possible reason for failure to detect implicit memory may be that sample sizes are not large enough to detect an effect. It has been suggested that the reason for failure of a "perfectly conducted" anaesthetic could be related to a notional Gaussian distribution of sensitivity to anaesthesia which allows a period of wakefulness for a patient lying in the upper tail of the distribution.[24] This would be relevant to the proposal that some individuals may be more sensitive to input, hence the sample size would need to be very large to include and detect them.

Third, it is conceivable that detection of implicit memory during anaesthesia may require even more sensitive tests, although the methodology of testing has been refined over the years; past methods included free-recall testing,[13] cued-recall testing[25] and word recognition tasks.[26] A later modification avoided the recall dependence on the circumstances of learning.[27] In our study using category generation, an attempt was made to optimize conditions for memory by avoiding benzodiazepine premedication,[28] prefacing the test words with instruction to attend, and by presenting information at times of likely maximal stimulation. We deliberately avoided testing explicit memory first as this may impede the subsequent detection of implicit memory.[7] Assessment of implicit memory was carried out within 36 h, as recommended by Merikle and Daneman.[29]

Future studies may consider several other aspects of methodology. Our study may be criticized for the lack of blinding as the investigators were aware of the words chosen, having been involved in the preliminary procedure to select them. However, this is unlikely to have affected our results. In selecting the target words for such studies, there should be no association between two target words (e.g. green and grape or orange and lemon), which might lead to their generation as a pair, regardless of whether they had both been primed. No particular association was evident in this study when sequences were examined. Methodologically, it might have been preferable to match priming targets for probability of their production in control conditions. However, their selection as relatively low frequency examples of the category was made to ensure that there was scope for priming effects to occur.

The relative ease with which categories are generated may need to be considered. In this population, colours were generated more easily than either fruits or vegetables. This was particularly interesting in the pre-induction group who were exposed to both colours and fruits and perhaps this implies less central processing for storage and generation of this particular category. To reduce type 1 errors, categories which are generated less well should be used for target words rather than control words.

Future studies using category generation may also consider evidence that the modalities for presentation and retrieval of information should be the same, as implicit memory may be very sensitive to change in modality.[30] State dependent learning (retrieval is dependent on the circumstances of learning being recreated at the time of recall) may have an effect on memory.[31] Tone of voice[32] during presentation of information to the patient (urgency/crisis) may provoke increased sympathetic stimulation but is still suppressed at less than 1 MAC for volatile agents.[23]

In this study, apart from successful priming in the pre-induction group, the only consistent trend (although not statistically significant) was the poorer recall of target words by the recovery group. This was surprising as, at the time of auditory stimulus, they appeared to be almost awake and were reacting to a tracheal tube or laryngeal mask in a vigorous manner. As this group was similar to the others in the production of control words, their inferior generation of target words may reflect the proposal that information presented at a time of noxious stimulus may be repressed.[33]

Finally, although there is a suggestion to the contrary,[34] this study was based on the reasonable hypothesis that implicit memory is located in a continuum between explicit recall and no recall, as described by Jones and Konieczko[35] and recently reiterated with substantial evidence.[36] The final possibility remains that implicit memory does not occur in these circumstances. Despite the timing of the stimulus, implicit memory could not be located in this group of patients. Reliable replication of positive results in this field is proving difficult, but in the words of Altman and Bland[37] "absence of evidence is not evidence of absence". However, the occurrence of implicit memory in the adequately anaesthetized patient is proving difficult to substantiate.

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Comparison of S(−)-bupivacaine with racemic (RS)-bupivacaine in supraclavicular brachial plexus block†

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Summary

Bupivacaine is used widely as a local anaesthetic but has potential for severe cardiovascular and central nervous system (CNS) toxicity. It has an asymmetric carbon atom giving it a chiral centre, and the commercial preparation is a racemic mixture of its two enantiomers: dextro or R(+)-bupivacaine and levo or S(−)-bupivacaine. Preclinical studies have demonstrated reduced cardiotoxicity and CNS toxicity for S(−)-bupivacaine. In this study we have compared the clinical efficacy of S(−)-bupivacaine with racemic RS-bupivacaine for supraclavicular brachial plexus block in 75 patients undergoing elective hand surgery. Patients received 0.4 ml kg^{-1} of either 0.25% or 0.5% S(−)-bupivacaine or 0.5% RS-bupivacaine in a randomized, double-blind study. Clinical assessments of sensory and motor block were performed at regular intervals. There were no significant differences in onset time, dermatomal spread or duration of both sensory and motor block between the three groups (the power of the study was 81% to detect a 4-h difference in duration). Duration of sensory block was prolonged with wide inter-patient variation: 892 (SD 250) min, 1039 (317) min and 896 (284) min for 0.25% S(−)-bupivacaine, 0.5% S(−)-bupivacaine and 0.5% RS-bupivacaine, respectively. There were no differences in the overall success rate of the technique. We conclude that S(−)-bupivacaine was suitable for local anaesthetic use in brachial plexus block anaesthesia. (*Br. J. Anaesth.* 1998; **80**: 594–598)

Keywords anaesthetic techniques, regional, brachial plexus; anaesthetics local, bupivacaine; anaesthetics local, stereoisomers

Bupivacaine is a long-acting local anaesthetic used widely in modern anaesthetic practice. It is well recognized that inadvertent i.v. administration or administration of toxic doses by another route can result in severe central nervous system (CNS) toxicity and cardiovascular collapse, with potentially fatal arrhythmias. Albright's editorial in 1979 discussed six cases in which bupivacaine was implicated in sudden cardiovascular collapse (and subsequent death in one obstetric patient) after clinical doses of bupivacaine.[1] More recent cases include an overdose of bupivacaine resulting in convulsions and ventricular tachycardia,[2] and continuous caudal infusions in children causing convulsions and arrhythmias.[3] Bupivacaine is contraindicated in i.v. regional anaesthesia (Bier's block).[4] These cases and many unpublished anecdotal instances of bupivacaine toxicity result in the continuing search for new and safer agents for clinical use.

Bupivacaine is a chiral compound.[5] It contains an asymmetric carbon atom giving it a chiral centre, about which the molecule can rotate forming different enantiomers. Bupivacaine exists as two enantiomers: levo or S(−)-bupivacaine and dextro or R(+)-bupivacaine, and is commercially available as a racemic (RS) mixture of both enantiomers. The enantiomers have identical physical and chemical properties but increasing evidence suggests enantiomer selectivity in both pharmacodynamics and pharmacokinetics.

S(−)-bupivacaine has been shown to have less inherent toxicity than R(+)-bupivacaine. Preclinical data from small mammals demonstrated higher LD_{50} values (1.2–3.3 times) and convulsion thresholds (1.7 times) compared with R(+)-bupivacaine.[6] Cardiotoxicity (widened QRS and arrhythmias, including AV blockade, ventricular tachycardia and ventricular fibrillation) has been shown to be 3–4 times more likely after R(+)-bupivacaine than S(−)-bupivacaine in isolated rabbit hearts.[7] In a study in 12 rats given R(+)-bupivacaine 2 mg kg^{-1}, all animals became apnoeic, bradycardic, hypotensive and died, whereas all 12 rats treated with S(−)-bupivacaine continued to breathe and only four developed mild bradycardia.[8] Studies in sheep have shown a reduced incidence, severity and duration of arrhythmias after S(−)-bupivacaine compared with RS-bupivacaine.[9] The convulsion threshold for S(−)-bupivacaine was 1.25–1.5 times higher than that for RS-bupivacaine.[10] Human volunteer investigations have also demonstrated differences in cardiotoxicity,[11] with 40–60% less reduction in myocardial contractility, as measured by acceleration index, stroke index and ejection

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Table 1 Patient characteristics (mean (SD or range))

	0.25% S(−)-bupivacaine	0.5% S(−)-bupivacaine	0.5% RS-bupivacaine
n	25	26	23
Age (yr)	53 (19–84)	56 (25–75)	55 (26–81)
Sex (M/F)	15/10	19/7	14/9
Weight (kg)	72 (12)	72 (15)	68 (14)
Height (cm)	171 (12)	171 (11)	167 (9)

fraction, after infusion of S(−)-bupivacaine compared with RS-bupivacaine.

Therefore, it appears that S(−)-bupivacaine has a significantly reduced potential for cardiovascular and CNS toxicity compared with RS-bupivacaine. In this randomized, double-blind study, we have compared the clinical efficacy of S(−)-bupivacaine with RS-bupivacaine in patients undergoing hand surgery under brachial plexus block.

Patients and methods

After obtaining approval from the local Medical Research Ethics Committee and written informed consent, we studied 76 patients undergoing elective hand surgery (mainly for Dupuytren's contracture or joint replacement) recruited from two centres. Patients were more than 18 yr of age and ASA I–III. Exclusion criteria included women who were pregnant, lactating or of childbearing potential and not using adequate contraceptive methods. Patients with severe renal, hepatic, respiratory or cardiac disease, drug or alcohol abuse or with neurological, psychiatric or neuromuscular disorders were also excluded.

On recruitment to the study, a blood screen for haematology measurements, urea and electrolyte concentrations, liver function tests, routine dipstick urinalysis and a 12-lead ECG were performed. Patients were allocated randomly, in a double-blind manner, to one of three groups: 0.25% or 0.5% S(−)-bupivacaine or 0.5% RS-bupivacaine (Marcaine, Astra).

Approximately 1 h before anaesthesia, patients were premedicated with temazepam 10–20 mg. On arrival in the anaesthetic room, i.v. access was established and standard monitoring commenced. An additional 16-gauge i.v. cannula was inserted into the contralateral antecubital fossa in 31 patients to allow multiple blood samples to be obtained for pharmacokinetic studies (data not yet available).

A single, experienced anaesthetist in each of the two centres performed the supraclavicular brachial plexus blocks. A 22-gauge insulated, short-bevelled needle was used with a nerve stimulator and the current reduced until appropriate twitching of the hand was achieved at 0.4 mA. After a negative aspiration test, 0.4 ml kg^{-1} of the study drug was injected over 1 min, with repeat aspirations every 5 ml. Assessments of the resulting block and haemodynamic variables were recorded as described below. After 30 min, if the block was considered to be adequate, surgery commenced. The patient was sedated, if requested, using infusion of propofol. If the block was considered to be inadequate for surgery, the patient was given a general anaesthetic using infusion of propofol with bolus doses of fentanyl 50 µg, as required.

Assessments were carried out at 2, 5, 10, 15, 20, 25 and 30 min, every 30 min until 5 h and hourly thereafter until the block had completely worn off, with time 0 min being the time of completion of the injection. Sensory block was measured as loss of pinprick sensation using the blunt end of a 27-gauge dental needle. Dermatomes C5 to T1 were assessed. Onset time was the time to first loss of pinprick sensation in any dermatome. Duration of sensory block was the time from onset to complete recovery of sensation. Motor block was recorded using a three-point scale (0=no paralysis, 1=difficulty in raising the shoulder and weakness of the hand, 2=inability to move upper limb). Onset time was the time to first loss of motor power. Duration of motor block was the time from onset to complete recovery of motor power. Heart rate and arterial pressure were also recorded at these times. An overall assessment of the quality of the block was made on a three-point scale: 0=complete failure; 1=unsatisfactory block (inadequate analgesia, inadequate relaxation or patient requires a general anaesthetic because of agitation or restlessness) and 2=satisfactory block. For statistical analysis, complete failure and unsatisfactory block were considered together as failures and compared with the successes (satisfactory block).

Postoperative analgesia comprised co-proxamol, two tablets 6-hourly, or morphine 10 mg i.m., 4-hourly, as required. Prochlorperazine 12.5 mg i.m. was given if required for nausea or vomiting.

At 24 h after surgery, a repeat blood screen for haematology measurements, urea and electrolyte concentrations, liver function tests, urinalysis and a 12-lead ECG were obtained. A follow-up telephone call was made to the patients 3–7 days after discharge to enquire about adverse events.

The results were analysed using the statistical package SAS (v6.07). The power of the study was calculated using an estimate of between-subject variability from a previous study (i.e. an SD associated with duration of sensory block of 5 h[12]). For a difference between groups in duration of sensory block of 4 h, the power of the study was 81%. Analysis of variance and the Student's *t* test were used to compare

Table 2 Sensory and motor block (mean (SD) on median (range))

	0.25% S(−)-bupivacaine	0.5% S(−)-bupivacaine	0.5% RS-bupivacaine
Sensory block			
n	25	24	22
Onset (min)	7 (6)	6 (5)	8 (8)
Duration (min)	892 (250)	1039 (317)	896 (284)
Motor block			
n	25	24	21
Onset (min)	9 (17)	5 (5)	6 (6)
Duration (min)	847 (276)	1050 (325)	933 (205)
Max. grade	2 (1–2)	2 (0–2)	2 (0–2)

Table 3 Sensory block at different dermatomes (median (range))

	0.25% S(−)-bupivacaine	0.5% S(−)-bupivacaine	0.5% RS-bupivacaine
T1			
n	19	21	17
Onset (min)	20 (2–240)	15 (2–150)	15 (2–720)
Duration (min)	658 (225–1115)	860 (5–1918)	825 (60–1185)
C8			
n	19	23	20
Onset (min)	15 (2–240)	10 (2–180)	13 (2–120)
Duration (min)	658 (60–1125)	895 (95–1498)	775 (170–1355)
C7			
n	23	21	20
Onset (min)	15 (2–120)	5 (2–60)	15 (2–120)
Duration (min)	635 (130–1180)	895 (160–1370)	773 (150–1120)
C6			
n	24	24	20
Onset (min)	10 (2–150)	15 (2–150)	13 (2–210)
Duration (min)	717 (235–1370)	803 (165–1258)	799 (60–1318)
C5			
n	23	23	20
Onset (min)	20 (2–150)	15 (2–150)	18 (2–240)
Duration (min)	720 (285–1420)	875 (270–1915)	810 (50–1258)

Table 4 Overall success of block (number of patients (%)). Groups 0 and 1 were considered together as treatment failures and group 2 as treatment success. No significant differences between groups

	0.25% S(−)-bupivacaine	0.5% S(−)-bupivacaine	0.5% RS-bupivacaine
Satisfactory block (2)	17 (68%)	21 (80%)	17 (74%)
Unsatisfactory block (1)	8 (32%)	3 (12%)	4 (17%)
Complete failure (0)	0	2 (8%)	2 (9%)

the groups after the Shapiro–Wilk test confirmed parametric data. The Kruskal–Wallis non-parametric analysis of variance and *Z* test were used for the remaining analyses. To compensate for multiple comparisons, a sequentially rejective Bonferroni–Holm method was used. Logistic regression was used to analyse the quality of block. All tests used a significance level of 5%.

Results

We studied 76 patients, of whom two were withdrawn. One patient was withdrawn before administration of the study drug because of pleuritic chest pain occurring while attempting to localize the brachial plexus. No subsequent pneumothorax or other sequelae were found. The other patient had what appeared to be i.v. injection of local anaesthetic (0.5% RS-bupivacaine) despite negative aspiration tests. After administration of approximately two-thirds of the injection, the patient lost consciousness and developed generalized twitching consistent with CNS toxicity. This was associated with sinus tachycardia and hypertension, but not hypoxia. The patient received 100% oxygen by face mask and propofol 40 mg. The episode resolved after 2–3 min with no sequelae. The characteristics of the remaining 74 patients are given in table 1. There were no differences between groups.

There were no significant differences between groups in onset time or duration of sensory block (tables 2, 3). There was a tendency for 0.5% S(−)-bupivacaine to have a longer duration of block. Spread of sensory block was similar in each group with the higher dermatomes being blocked more reliably.

Nearly all patients (except one) who achieved sensory block achieved motor block (table 2). Grade 2 (complete paralysis) was the most common grade reached. There were no significant differences between groups in onset time, maximum grade or duration of motor block. As with sensory block there was a tendency for 0.5% S(−)-bupivacaine to have a longer duration.

Four patients were assessed as complete failures (two each in the 0.5% S(−)-bupivacaine and 0.5% RS-bupivacaine groups) (table 4). These were caused by complete failure of the technique or inadequate block for surgery. General anaesthesia was required in these cases. Another 10 patients required general anaesthesia (eight in the 0.25% S(−)-bupivacaine group and two in the 0.5% RS-bupivacaine group). These were for patients with unsatisfactory blocks, as described above. There were no significant differences between groups.

There were no significant differences between groups in heart rate or arterial pressure for the first 30 min after drug administration. There were small reductions in heart rate and arterial pressure during this period (ns) but these were not clinically significant.

There were no clinically significant ECG changes in the perioperative period. Analysis of screening and postoperative ECG showed no evidence of dose-related trends or changes. There was no evidence of drug or dose-related changes in haematological, biochemical or urinalysis variables. One patient (0.5% S(−)-bupivacaine) complained of paraesthesia in the postoperative period. This was related to the surgical procedure. One patient had a major adverse event (this woman received what was suspected to be i.v. injection of 0.5% RS-bupivacaine, as described above). There were no other adverse events.

Discussion

We have demonstrated that S(−)-bupivacaine was suitable for brachial plexus block anaesthesia. There were no significant differences in sensory or motor block between the three groups. We were unable to demonstrate a dose–response effect with the two concentrations of S(−)-bupivacaine, although there was a tendency for 0.25% S(−)-bupivacaine to have a slower onset, shorter duration of action and lower overall success rate than 0.5% S(−)-bupivacaine or RS-bupivacaine. The power of the study was low, with an 81% chance of detecting a 4-h difference in duration and only a 56% chance of detecting a 3-h difference. There was wide patient variation in these blocks.[12] The SD of the duration of sensory block was more than 4 h. However, the long duration of sensory block illustrates the benefit of bupivacaine and its enantiomers in providing prolonged postoperative analgesia. The study showed that the higher dermatomes were blocked more consistently than the lower ones, as expected with the supraclavicular approach. The overall success rate for the anaesthetic technique was 68–80%. Supplementary nerve blocks, which may have increased this rate, were not possible as pharmacokinetic studies were also being performed.

There was one serious adverse event during the study. This patient received what was presumed to be i.v. injection of RS-bupivacaine (despite regular negative aspiration tests) and developed CNS and related cardiovascular (tachycardia and hypertension) side effects. Fortunately, these resolved rapidly and resulted in no subsequent morbidity. This case, however, illustrates the risks associated with administration of large doses of bupivacaine, even in experienced hands, and emphasizes the need for safer agents.

The major impetus behind the search for new and safer local anaesthetics is the known cardiovascular and CNS toxicity of existing drugs. The mechanism for the cardiotoxicity of bupivacaine is complex. There is evidence of direct and indirect depression of cardiac conduction and contractility. Bupivacaine produces local anaesthesia by block of sodium channels and this action is probably the main mechanism responsible for its cardiotoxicity. Blocking of the sodium channel in the isolated guinea pig heart by bupivacaine resulted in a reduction in the maximum rate of depolarization (*v*max) and a shortening of the duration of the action potential (AP).[13] Slowing the conduction of the AP resulted in increased PR intervals and QRS durations and encouraged re-entrant arrhythmias (ventricular ectopics, tachycardia and fibrillation). Studies suggest that compared with S(−)-bupivacaine, R(+)-bupivacaine has 2.4 times higher affinity for the cardiac sodium channel and dissociates from it twice as slowly.[14] This results in a longer dwell time at the sodium channel making it potentially more arrhythmogenic. This study also showed that *v*max and AP duration are decreased more, and recovered more slowly with R(+)-bupivacaine compared with S(−)-bupivacaine. R(+)-bupivacaine had a higher potency (1.6 times) in blocking inactivated cardiac sodium channels, as shown in isolated animal heart studies.[15] Cardiac potassium channels have also been implicated in the cardiotoxicity of bupivacaine: R(+)-bupivacaine has been shown to be seven times more potent at blocking human cardiac potassium channels than S(−)-bupivacaine.[16] There is evidence that the CNS plays a role in the cardiotoxicity produced by bupivacaine. This indirect cardiotoxicity is also enantiomer selective with R(+)-bupivacaine having a greater depressant effect on the cell firing rate of the nucleus tractus solitarius and therefore the cardiovascular and respiratory centres of the brain.[8] Therefore, R(+)-bupivacaine appears to be the main culprit in the toxicity produced by RS-bupivacaine by its effect on the CNS and cardiac sodium and potassium channels.

This reduced toxicity does not appear to be at the expense of nerve blocking activity. In small mammals, the *in vitro* and *in vivo* efficacy of S(−)-bupivacaine and R(+)-bupivacaine was similar, although the duration of anaesthesia after subcutaneous infiltration was longer for S(−)-bupivacaine.[6] Apps and Reynolds' volunteer study of intradermal infiltration demonstrated that S(−)-bupivacaine, unlike R(+)-bupivacaine, had some vasoconstrictor activity.[17] This may explain the longer duration of action found in these studies. This contrasts with a recent study investigating the effects of S(−)-bupivacaine and (RS)-bupivacaine on human umbilical veins in which vascular activities were found to be similar.[18] Our study did not demonstrate any significant differences in duration of sensory or motor block between S(−)-bupivacaine and RS-bupivacaine. Further work investigating this feature of S(−)-bupivacaine is required.

Bupivacaine is used widely because of its long duration of action, differential block and, in obstetric use, lack of adverse neonatal neurobehavioural effects. The chiral nature of bupivacaine has been known for many years but it is only recently that the S(−)-enantiomer has been developed for clinical use. We have demonstrated that S(−)-bupivacaine was suitable for use in brachial plexus block anaesthesia. This, together with the reduced toxic potential compared with (RS)-bupivacaine, suggests that S(−)-bupivacaine may increase the margin of safety for regional anaesthesia.

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Cardiovascular disturbances caused by extradural negative pressure drainage systems after intracranial surgery

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Summary

Extradural drainage systems connected to a vacuum device for preventing postoperative haematoma formation are often used in neurosurgical practice. Cardiovascular complications, including bradycardia or low arterial pressure caused by intracranial hypotension, have been described associated with their use. We have investigated the relationship between the negative pressure applied to extradural drainage systems and intracranial pressure (ICP), and analysed the effects of negative pressure of the drains on systolic (SAP), diastolic (DAP) and mean (MAP) arterial pressures and on heart rate (HR). We studied prospectively 15 patients undergoing neurosurgery for supratentorial tumours or aneurysms. Transient decreases in ICP (P<0.001) and HR (P<0.001), with no clinical effects, were observed after connecting the vacuum device to the drain. There were no significant changes in SAP, DAP or MAP. (*Br. J. Anaesth.* 1998; **80**: 599–601)

Keywords: equipment, extradural drainage systems; heart, heart rate, surgery, neurological; cardiovascular system, effects

Increased intracranial pressure (ICP) can cause bradycardia and hypertension as a result of the stimulus of pressure or stretch, or both, of the brainstem, referred to as Cushing's response.[1 2] However, haemodynamic changes associated with intracranial hypotension have seldom been described. Most reports are based on clinical observations. Many neurosurgical procedures, such as surgery for brain tumours and haematomas, require the use of extradural or epicranial drains, which are frequently connected to a vacuum device for preventing haematoma formation or drain obstruction. Severe cardiovascular disorders (bradycardia, asystole or arterial hypotension) related to their use have been published.[3 4]

The aim of our study was to investigate the effect on ICP of the negative pressure achieved by an extradural drainage system and its consequences on heart rate (HR), systolic (SAP), diastolic (DAP) and mean (MAP) arterial pressures.

Patients and methods

We studied 15 consecutive patients, aged 28–65 yr, ASA I–II, undergoing elective supratentorial tumour and aneurysm surgery. The study was approved by the Institutional Human Ethics Committee and patient consent was obtained.

On arrival in the operating room, patients were premedicated with midazolam 0.02–0.03 mg kg^{-1} i.v. Anaesthesia was induced with thiopental 4–6 mg kg^{-1}, fentanyl 3–4 µg kg^{-1} and lidocaine 1.5 mg kg^{-1}. Vecuronium (up to 0.2 mg kg^{-1}) was administered to aid tracheal intubation. Anaesthesia was maintained with isoflurane (0.2–0.6% end-tidal concentration) and 60–70% nitrous oxide in oxygen, and fentanyl 1–2 µg kg^{-1} h^{-1}. Neuromuscular block was produced with vecuronium 0.08–0.1 mg kg^{-1} h^{-1}. Controlled mechanical ventilation (Servo 900 C ventilator) was adjusted to maintain end-tidal carbon dioxide partial pressure (PE'_{CO_2}) at 3.7–4.3 kPa.

Before induction of anaesthesia, we monitored invasively radial arterial pressure, HR, electrocardiogram (leads II and V5) and arterial haemoglobin oxygen saturation (Sp_{O_2}) using a Siemens Sirecust 730 monitor. PE'_{CO_2} was measured with an Engström Eliza carbon dioxide analyser, and neuromuscular function was monitored with a Microstin Plus peripheral nerve stimulator. After induction of anaesthesia, we inserted a nasopharyngeal thermometer, oesophageal stethoscope and central venous catheter.

The skin was infiltrated with 0.5% bupivacaine before the start of surgery. Mannitol 0.5 g kg^{-1}, sometimes associated with a loop diuretic, was administered. MAP was 80–110 mm Hg during surgery.

After tumour resection or aneurysm clipping, and before totally closing the dura mater, the neurosurgeon placed a subdural fibreoptic transducer attached to a Camino monitor (Camino 420 OLM) for continuous recording of ICP. ICP recording was started at the end of surgery.

In all patients the dura mater was sutured in a watertight manner, and when there remained a space between the brain and dura mater, it was filled with saline solution infused without applying pressure. Before bone flap replacement, an extradural drain was positioned in the extradural space, as far as

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possible from the ICP sensor. The drain was then connected to a suction system (Red-O-Pack, Vygon, France) to which subatmospheric vacuum pressure had been applied. The drainage system was stabilized at the end of the procedure and maintained for the first 24 h, as indicated by the surgeon. Negative pressure was applied only after surgical closure and wound dressing. The pressure applied to the vacuum device was measured by a manometer attached to the vacuum system.

ICP and haemodynamic variables (SAP, DAP, MAP and HR) were recorded continuously at the end of operation, before connecting the drain to the vacuum system, after connection, while the patient was still anaesthetized, in the supine position, and with slight elevation of the head (10°). Peak values of these variables, and time after vacuum application were recorded. Duration of these changes was also noted.

For statistical analysis, we used the log-transformation and the Shapiro–Wilks test to study the normality of the data. This demonstrated a non-normal distribution. Data were analysed using the non-parametric Wilcoxon test for paired samples. We also used covariance analysis (ANCOVA) with repeated measures and multiple regression analysis to evaluate the relation between decrease in HR (ΔHR) and decrease in ICP (ΔICP) after applying negative pressure to the extradural drainage system. Differences were considered statistically significant when $P<0.05$.

Results

Patient data (age, sex, weight), duration of surgery, duration of anaesthesia, negative pressure values in the vacuum system and type of surgical procedure are presented in table 1.

A decrease in SAP, MAP and an increase in DAP with regard to baseline values was observed immediately after application of the vacuum to the drainage system, but these differences were not significant (table 2). There were significant decreases in HR and ICP ($P<0.001$) after applying negative pressure (table 2). After application of the vacuum system, ICP decreased to subatmospheric values in all patients. Mean intervals from application of the vacuum system to measurement of the lower values of ICP and HR were 70 (range 4–175) and 21 (8–91) s, respectively. The changes in HR and ICP were temporary and returned to those obtained before application of the negative pressure at mean times of 32 (18–75) s and 97 (20–242) min, respectively.

We found no correlation between the decrease in HR (ΔHR) and decrease in ICP (ΔICP) after application of negative pressure to the extradural drainage system.

Table 1 Patient characteristics (median (range))

n	15
Age (yr)	56 (28–65)
Sex (M:F)	9:6
Weight (kg)	68 (57–86)
Negative pressure (cm H_2O)	75 (65–80)
Duration of anaesthesia (min)	315 (240–450)
Duration of surgery (min)	210 (150–360)
Surgican procedure (excision of tumour:aneurysm clipping)	8:7

Table 2 Systolic (SAP), diastolic (DAP) and mean (MAP) arterial pressures, and heart rate (HR) and intracranial pressure (ICP) before and after placement of an extradural drain connected to a vacuum system (median (range))

	Before negative pressure	Immediately after connection of vacuum system	*P*
SAP (mm Hg)	124 (107–145)	122 (107–142)	ns
MAP (mm Hg)	91 (76–101)	90 (75–102)	ns
DAP (mm Hg)	65 (60–78)	71 (60–82)	ns
HR (beat min^{-1})	65 (55–90)	58 (51–87)	<0.001
ICP (mm Hg)	4 (1–10)	−5 (−18 to −2)	<0.001

Discussion

In this study, placement of an extradural drain connected to a vacuum system at the end of intracranial surgery produced a sudden decrease in ICP that reached subatmospheric values in all patients. This sudden reduction in ICP was caused by transmission of negative pressure from the area (extradural or epicranial space) where the drain was located to the subdural space. Severe decreases in ICP may cause a rostral shift of the brain which is reversed when ICP returns to its previous values. Physical properties of brain tissues may preclude this shift, even during suction.[4–8]

In our study, a significant decrease in HR without changes in arterial pressure was observed immediately after connecting the vacuum system and before reaching the peak decrease in ICP. However, there was a rapid return to pre-suction values. These data are in agreement with those of Gilsanz and colleagues[7] who observed a significant decrease in HR 3 min after connecting the vacuum system to the epicranial drain. However, in our study, the effect of the negative pressure on ICP and HR was more immediate.

Several reports have described severe bradycardia or arterial hypotension, or both, after connection of negative suction pressure to extradural[6 9] or epicranial[5 10] drains after craniotomy. These haemodynamic changes were similar to those observed when ICP suddenly decreased after decompression of hydrocephalic ventricles.[11 12] Rapid removal of cerebrospinal fluid (CSF) in patients with obstructive hydrocephalus or intracranial application of negative pressure via an extradural or epicranial drain, may lead to a sudden state of intracranial hypotension resulting in a rostral movement of the brain or brainstem nuclei responsible for the changes in cardiac rhythm or arterial hypotension, or both.[4 5 7 12 13] Reduction in HR secondary to a sudden decrease in ICP may be caused by a mechanism similar to Cushing's response to intracranial hypertension.[9] Several authors[1 2] have demonstrated that the haemodynamic features of Cushing's response can be produced by electrical stimulation or distension of tissues within a thin strip of brain along the floor of the fourth ventricle in the rostral medulla and caudal pons, the efferent limb of the bradycardic response being the vagus nerve. The observed cardiovascular disorders reverse on releasing the negative pressure or by filling the ventricles with saline solution after decompression in hydrocephalus.[5 6 9 11] In our study, we observed no correlation between HR and ICP values, which would indicate the contribution of other factors in the decrease in HR. Application of a strong negative pressure to the drainage system, reduction of the brain bulk at the end of craniotomy (provoked by the use of mannitol, hyperventilation, CSF leakage during surgery and tumour resection), administration of β blockers and stretching on the dura mater may lead to important haemodynamic disturbances with subsequent clinical consequences.[5 10 14 15]

In our study, the use of an extradural drain connected to a vacuum system after craniotomy had no clinically significant adverse effects. However, there exists the possibility of an important decrease in ICP which could provoke severe cardiovascular consequences. Therefore, haemodynamic variables must be monitored closely and controlled at the time of applying negative pressure to the drain. If severe bradycardia occurs, it should be managed promptly with anticholinergic agents and closure of the drainage system.

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Preoperative nocturnal desaturations as a risk factor for late postoperative nocturnal desaturations

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Summary

Severe postoperative hypoxaemia during sleep may increase the risk of postoperative cardiovascular complications. We hypothesized that the severity of hypoxic episodes after surgery are related to the presence of preoperative sleep-disordered breathing (SDB). We tested this hypothesis in a multicentre study designed to elucidate the major risk factors for development of postoperative nocturnal desaturations. We performed overnight oximetry before operation and for one night between the second and fourth day after operation in 80 patients undergoing major surgery. We calculated oximetry variables such as oxygen desaturation index (ODI), defined as the number of oxygen desaturations exceeding 4% below baseline, percentage time spent at Sp_{O_2} <90% (CT_{90},%) and lowest Sp_{O_2} value. After operation, although the change in ODI was not significant (P=0.34), deterioration in CT_{90} and lowest Sp_{O_2} values were significant (P=0.036 and P=0.007, respectively). Multivariate analysis of possible risk factors for postoperative desaturations revealed that preoperative hypoxaemia and apnoea witnessed by others were highly correlated with postoperative hypoxaemia. (*Br. J. Anaesth.* 1998; **80**: 602–605)

Keywords: surgery, postoperative period; complications, sleep-disordered breathing; hypoxaemia; oxygen, saturation; measurement techniques, oximeters

Postoperative sleep-disordered breathing (SDB) is clinically significant because of its potential association with postoperative complications such as mental dysfunction, myocardial infarction and unexplained sudden postoperative death.[1–4] The occurrence of these complications may increase with increases in severity and frequency of nocturnal hypoxic episodes. Accordingly, identifying the risk factors of severe postoperative hypoxaemia during sleep may be very important in terms of safety management of postoperative patients in the general ward. Obstructive sleep-apnoea (OSA) is characterized by repetitive pharyngeal airway occlusion during sleep leading to severe episodic hypoxaemia.[5] Recent epidemiological evidence indicates that OSA is a relatively common disorder affecting 2–16% of the adult population.[6–10]

Although postoperative desaturation has been reported in patients without preoperative SDB or OSA,[11 12] hypoxic episodes may be more serious in these patients. A high prevalence of hypertension and ischaemic heart disease in patients with SDB may further increase the risk of cardiovascular complications after surgery.[13–16]

Therefore, we tested the hypothesis that development of postoperative nocturnal desaturation is associated with the presence of preoperative SDB in a multicentre study involving three Japanese university hospitals, and examined if the severity of nocturnal desaturation in these patients increases after surgery.

Patients and methods

We studied 90 patients undergoing elective surgery at three different hospitals. We excluded patients undergoing surgical procedures of the upper airway and those who were expected to receive oxygen therapy up to day 4 after operation. We attempted to enroll patients with SDB as much as possible. Informed consent was obtained from each subject, and the study was approved by the Ethics Committee of each hospital.

Routine perioperative management (pain control and oxygen therapy) of patients was unaltered except for administration of additional nocturnal oxygen therapy during severe desaturation on nights 2 to 4 after operation. Eight subjects were excluded because of technical failures and two because they developed postoperative respiratory failure.

Nocturnal oxygenation was evaluated by a pulse oximeter (N-3000, Nellcor, Carlsbad, CA, USA). All subjects were instructed to attach the finger probe of the oximeter before going to sleep and to remove the probe on awakening. Digital readings of arterial oxygen saturation Sp_{O_2} and heart rate were stored every 5 s in the oximeter memory. The stored data were displayed on a computer screen (SatMaster, EMG Scientific, Los Angeles, CA, USA). The program allowed exclusion of artefactual desaturation caused by changes in signal amplitude.[17] A computer program developed at Chiba University calculated oxygen desaturation index (ODI), defined as the

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Table 1 Patient characteristics and details of surgery and anaesthesia (median (range) or number). Anaesthesia 1= regional (+ inhalation) anaesthesia, anaesthesia 2=inhalation anaesthesia, surgery 1=thoracic or abdominal surgery, surgery 2=other, including laparoscopic abdominal surgery

n	80
Sex (M/F)	35/45
Age (yr)	54 (25–87)
Height (m)	1.58 (1.30–1.77)
Weight (kg)	55 (33–82)
Body mass index (kg m^{-2})	22.3 (15.1–28.8)
Neck circumference (cm)	34 (28–43)
Pa_{O_2} (kPa) (Fi_{O_2}=0.21)	11.7 (8 9–15.7)
%VC (% predicted)	101 (65–141)
%FEV$_1$ (%)	85 (42.3–121)
ASA status	2 (1–3)
Anaesthesia 1/2	20/60
Surgery 1/2	34/46
Operation duration (h)	3.0 (1.0–12.3)
Extradural morphine (mg day^{-1})	0 (0–4.5)

number of oxygen desaturation episodes exceeding 4% below baseline per hour, percentage of time spent at Sp_{O_2} <90% (CT$_{90}$,%) and lowest Sp_{O_2} value. Baseline Sp_{O_2} was defined as the highest Sp_{O_2} which lasted for at least 10 s in a 2-min period. In general, ODI is related to the number of apnoeic or hyponoeic episodes while CT$_{90}$ and lowest Sp_{O_2} are influenced by the duration of episodes and baseline Sp_{O_2}.

Sedatives were not prescribed on the night of the study. Overnight oximetry was repeated on one night between the second and fourth day after operation.

Possible risk factors responsible for late postoperative desaturation were recorded, including: sex, age, height, weight, body mass index (BMI), neck circumference, ASA status, Pa_{O_2}, %VC, %FEV$_1$, type of anaesthetic, type of surgical procedure, duration of operation and dose of extradural morphine. Probability of the presence of SDB was scored by evidence of clinical symptoms, such as habitual loud snoring, excessive daytime sleepiness and apnoea witnessed by others during sleep. Excessive daytime sleepiness was determined by the presence of extreme sleepiness during the day while watching television, driving a car or attending a meeting.

Differences in oximetric and other variables before and after surgery were compared using the Wilcoxon signed rank test. Correlations between postoperative ODI and the other variables were evaluated by the Spearman rank order test. To determine the major contributing factors to postoperative ODI, multivariate linear regression analysis was performed. A backward stepwise method was applied initially for the variables which had significant correlations with postoperative ODI. Results are expressed as median (range). P<0.05 was considered significant.

Results

Table 1 shows the patient characteristics of those who underwent nocturnal oximetry before and after surgery.

Figure 1 illustrates the changes in oximetric variables before and after surgery. Changes in ODI were variable but there was no significant increase in hypoxaemia after surgery (P=0.34) despite some patients showing marked increases in ODI. CT$_{90}$ and lowest Sp_{O_2} differed significantly (P=0.036 and P=0.007, respectively). Therefore, the severity of nocturnal hypoxaemia increased after surgery while the frequency of hypoxic episodes was unchanged.

Results of correlation analysis between postoperative hypoxaemia and other physiological and clinical variables are presented in table 2. There were significant correlations between obesity and development of postoperative hypoxaemia. Among the three typical clinical symptoms suggesting SDB, only apnoea witnessed by others correlated with postoperative hypoxaemia. We found the highest correlation between preoperative hypoxaemia and postoperative hypoxaemia (r=0.526). Using the significant variables in table 2, we performed multivariate linear regression analysis to determine the major contributing factors to postoperative ODI. A backward stepwise method produced a linear regression model with two highly significant variables, preoperative ODI and apnoea witnessed by others (table 3).

Discussion

We have performed nocturnal oximetry before and after surgery in a relatively large sample for the purpose of identifying risk factors for late postoperative hypoxaemia during sleep. We showed that preoperative nocturnal oxygenation worsened after surgery and postoperative hypoxaemia was best predicted by preoperative hypoxaemia and apnoea witnessed by others.

A major limitation of this study was the number of uncontrolled variables. Type of surgery, anaesthetic technique and postoperative analgesia varied

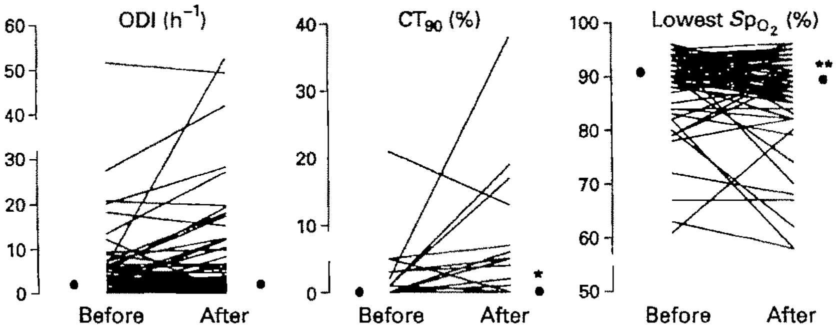

Figure 1 Results of nocturnal oximetry before and after surgery. ODI=Oxygen desaturation index defined as the number of desaturation episodes exceeding 4% below baseline per hour and CT$_{90}$=percentage time spent at Sp_{O_2} <90%. Before=2 days before surgery and after=1 night between the second and fourth day after operation. Each line represents the change in variable for each subject. Median values are shown by closed circles. *P<0.05 and **P<0 01 compared with before surgery.

Table 2 Correlation between postoperative hypoxaemia and clinical variables. Spearman rank order correlations were performed. ODI=Oxygen desaturation index defined as the number of oxygen desaturations exceeding 4% from baseline, CT_{90}=percentage of time spent at Sp_{O_2} <90%

Clinical variable	*r*	*P*
ASA status	0.139	0.222
Sex	−0.100	0.377
Age	0.100	0.379
Height	−0.125	0.273
Weight	0.302	0.007
Body mass index	0.345	0.002
Neck circumference	0.133	0.274
Pa_{O_2}	−0.183	0.131
%VC	−0.052	0.668
%FEV_1	−0.006	0.963
History suggesting SDB	0.204	0.072
Habitual loud snoring	0.198	0.081
Excessive daytime sleepiness	0.149	0.191
Apnoea witnessed by others	0.416	0.000
Preoperative nocturnal oximetry		
ODI	0.526	0.000
CT_{90}	0.457	0.000
Lowest Sp_{O_2}	−0.382	0.000
Type of anaesthetic	−0.252	0.026
Type of surgery	0.194	0.095
Duration of operation	0.009	0.946
Dose of extradural morphine	0.023	0.843

Table 3 Multivariate linear regression. ODI=Oxygen desaturation index

Variable	Estimate	SE	*t*	*P*
Constant	1.53	0.79	1.94	0.06
Preoperative ODI (h^{-1})	0.73	0.12	6.27	<0.001
Witnessed apnoea (0 or 1)	14.3	3.0	4.79	<0.001

randomly. The postoperative night studied varied from the second to the fourth night. All of these uncontrolled variables and the bias of the patient selection are likely to have affected the determination of risk factors for postoperative desaturations.

Our method was unable to elucidate whether obstructive or central apnoea–hypopnoea caused the observed nocturnal desaturations.[18 19] In addition, the presence of SDB may have been overlooked in some patients with lower ODI values. Further, total monitoring time used to calculate ODI may be greater than total sleep time, especially during postoperative periods when sleep is likely to be fragmented because of persistent pain, high fever and environmental noise. Therefore, we attempted to approximate total monitoring time to total sleep time by asking the subjects to remove the oximetry probe when they were not sleeping. This potential overestimation of total sleep time becomes more significant in patients with SDB who have a larger denominator in the calculation of ODI, possibly resulting in underestimation of postoperative ODI in patients with SDB. These methodological deficits may account for the great variability in the changes in ODI. Clearly, pre- and postoperative polysomnography is necessary to clarify this issue.

Preoperative hypoxaemia was the best predictor of postoperative hypoxaemia. Other significant factors such as obesity and apnoea witnessed by others were also predictive. Our data differed from those of Reeder and colleagues[12] who found that preoperative oximetry identified only a small proportion of patients at risk of postoperative SDB while all patients with preoperative SDB experienced SDB after operation. Differences in selection of subjects, body size or race may account for this. More recently, Gentil, Lienhart and Fleury[20] demonstrated that patients with a previous history of SDB were at risk of postoperative desaturations, and that preoperative questionnaires assessing daytime sleepiness were useful in predicting those who developed postoperative desaturations.

In summary, we have shown that preoperative episodic hypoxaemia and a history of witnessed apnoea were significant predictors of postoperative hypoxaemia.

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Relationship between difficult tracheal intubation and obstructive sleep apnoea

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Summary

The upper airway abnormalities predisposing to difficult tracheal intubation may also predispose to obstructive sleep apnoea (OSA). The potential association is important as both conditions increase perioperative risk and patients with a trachea that is difficult to intubate may need assessment for OSA. We determined if patients with difficult intubation are at greater risk of OSA and, if so, whether or not they have characteristic clinical or radiographic upper airway changes. We studied 15 patients in whom the trachea was difficult to intubate and 15 control patients. Each was evaluated clinically (Mallampati score, thyromental distance, neck circumference, head extension), polysomnographically (apnoea–hypopnoea index (AHI)) and radiographically (lateral cephalometry). AHI was greater in the difficult intubation group (mean 28.4 (SD 31.7)) compared with controls (5.9 (8.9)) ($P<0.02$); eight of 15 patients in the difficult intubation group and two of 15 in the control group had an AHI >10 ($P<0.03$). Difficult intubation, but not OSA, was associated ($P<0.05$) with a smaller thyromental distance and mandibular length, and greater soft palate length. Both difficult intubation and OSA were associated ($P<0.05$) with a greater Mallampati score, anterior mandibular depth, and smaller mandibular and cervical angles. OSA, but not difficult intubation, was associated ($P<0.05$) with increased neck circumference, tongue area and craniocervical angle, and decreased head extension, mandibular ramus length and atlanto-occipital distance. We conclude that difficult intubation and OSA are related significantly. They share anatomical features which act to reduce the skeletal confines of the tongue. Patients with OSA may compensate, when awake, by increasing craniocervical angulation, which increases the space between the mandible and cervical spine and elongates the tongue and soft tissues of the neck. (*Br. J. Anaesth.* 1998; **80**: 606–611)

Keywords: intubation tracheal, difficult; sleep apnoea; ventilation, apnoea; airway, anatomy; complications, obstructive sleep apnoea

Difficult tracheal intubation and obstructive sleep apnoea (OSA) are two common clinical problems which contribute to perioperative morbidity and mortality.[1–3] The reported incidence of failed tracheal intubation is 1 in 2300 in non-obstetric patients and 1 in 300 in obstetric patients.[4] OSA, characterized by repetitive partial or complete upper airway obstruction during sleep, has been estimated to affect 4% of men and 2% of women in middle age[5] and has been identified as a major health problem as a result of associated greater daytime sleepiness,[6] hypertension[7 8] and increased risk of cardiovascular[9 10] and cerebrovascular disease.[11]

Upper airway abnormalities have been described in both conditions. Clinically, a short thick neck,[12] limited head extension[13 14] and reduced thyromental distance[15] have been associated with difficult tracheal intubation, and oropharyngeal crowding and greater neck circumference with OSA.[16 17] A large tongue has been associated with both.[16 18] Radiographic studies of upper airway structure using lateral cephalometry have demonstrated craniocervical and mandibulohyoid abnormalities in each condition[19–23] but there has been no examination of their inter-relationship.

It has been suggested that in patients with OSA, the trachea may be difficult to intubate[2 24] and, conversely, those who have tracheas that are difficult to intubate may be at increased risk of OSA.[20 25] Shared upper airway abnormalities could provide the basis for such an association. However, the relationship between the two conditions has not been studied formally and remains undefined. If difficult intubation indicates a predisposition to OSA, it would be important to be aware of it as prompt identification and treatment could prevent associated morbidity and mortality in the perioperative period and beyond. Hence the aim of this study was to determine if patients who present with difficult tracheal intubation are more likely to have OSA and, if so, what upper airway abnormalities are shared by the two conditions.

Patients and methods

After obtaining approval from the hospital Ethics Committee, we recruited subjects from the

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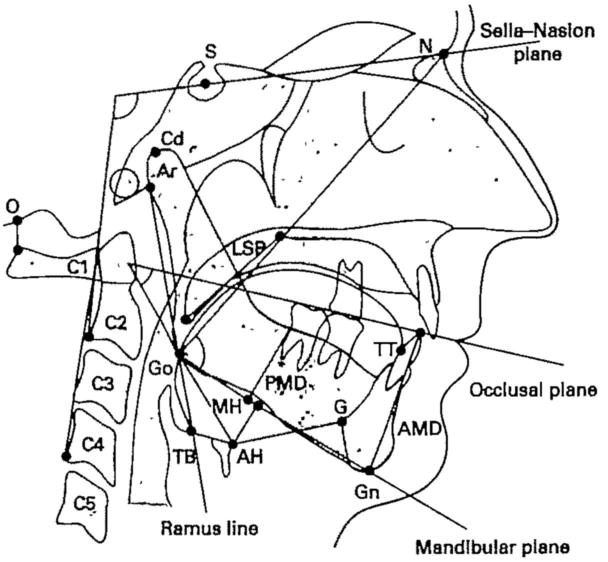

Figure 1 Diagrammatic representation of lateral cephalometric analysis showing relevant skeletal and soft tissue landmarks. Reference points: N=nasion; S=sella point; Cd=condylion; Ar=articulare; TT=tongue tip; TB=tongue base; Go=gonion; G=genial tubercle; Gn=gnathion; AH=anterior hyoid. Reference lines: sella–nasion plane (SNP)=through N and S; occlusal plane=through midpoint in incisor overbite and contact point of posterior molars in occlusion; mandibular plane=tangent to lower border of mandible through Gn; ramus line=tangent to posterior border of mandible through Ar. Measurements—skeletal (linear): AMD=anterior mandibular depth (Gn to tip of mandibular central incisor); PMD=posterior mandibular depth (perpendicular distance from mandibular plane to alveolar margin of mandible at position of posterior border of third molar); Go–Gn=mandibular length; Cd–Go=mandibular ramus length; O–C1=atlanto-occipital distance (vertical, from upper margin of posterior tubercle of C1 to base of skull); MH=mandibulohyoid distance (perpendicular, from AH to ML).Measurements—skeletal (angular): lower mandibular angle=angle between N–Go and mandibular plane; craniocervical angle=angle between SNP and line through posterosuperior aspect of dens and posteroinferior aspect of body of C2; cervical angle=angle between line through posterosuperior aspect of dens and posteroinferior aspect of body of C2 and line through posterosuperior aspect of dens and posteroinferior aspect of body of C4; occlusal–goniohyoid angle=angle between occlusal plane and line through Go and AH. Soft tissue: total tongue area=TT to TB (along superior border) to AH to G to TT; LSP=length of soft palate (from posterior nasal spine to tip of uvula).

anaesthetic department database, from the years 1993–1995, if they were recorded as difficult to intubate by a consultant anaesthetist (Cormack and Lehane[26] grade 4—no glottic structure visible on laryngoscopy). Patients with obvious craniofacial or cervical abnormalities requiring previous medical or surgical intervention and those undergoing head or neck surgery were excluded. Thirty-two subjects met the selection criteria and 17 agreed to participate in the study. Of these, we excluded two subjects who were already receiving treatment for diagnosed OSA; therefore, 15 subjects were included. Fifteen control subjects matched for age, sex, height and weight, and who were recorded as easy to intubate (Cormack and Lehane[26] grade 1—full view of glottic structures), were recruited from the same database. Each subject was assessed clinically, polysomnographically and radiographically (lateral cephalometry).

CLINICAL ASSESSMENT

Each subject was assessed clinically by a single observer (A. H.) before polysomnography and cephalometry. Oropharyngeal appearance was assessed using the modified Mallampati method.[4] The subject sat upright with the head in the neutral position, the mouth fully open and the tongue maximally protruded, and was instructed not to phonate. The oropharynx was inspected from the subject's eye level and the appearance classified as follows: class I, soft palate, fauces, uvula and tonsillar pillars visible; class II, soft palate, fauces and uvula visible; class III, soft palate and base of uvula visible; and class IV, soft palate not visible. Thyromental distance was measured from the thyroid prominence to the most anterior part of the chin, with the head fully extended.[15] External neck circumference was measured at the level of the cricothyroid membrane, with the head in the neutral position.[17] Head extension at the atlanto-occipital joint was assessed by measuring the angle traversed by the occlusal surface of the maxillary teeth, when the head was fully extended from a neutral position, using a goniometer.

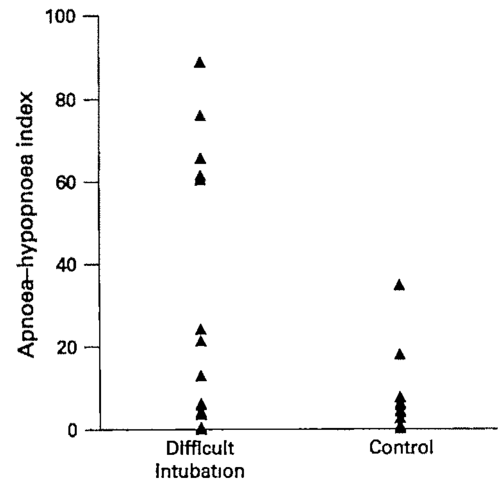

Figure 2 Apnoea–hypopnoea index (AHI) of each subject in the difficult intubation and control groups.

POLYSOMNOGRAPHY

Sleep stage (electroencephalogram (C4/A1), right and left electro-oculogram and submental electromyogram), oronasal airflow (thermistor), ribcage and abdominal wall motion (inductance plethysmography), arterial oxyhaemoglobin saturation (pulse oximetry), electrocardiogram and sound were recorded on a digital polysomnograph (Ultrasom, Nicolet Biomedical, Madison, USA). The polysomnograph was analysed by an experienced technologist who was blinded to the intubation status of the subject. Sleep stage was scored using the criteria of Rechtschaffen and Kales.[27] Apnoea was defined as cessation of oronasal airflow for more than 10 s. Continued ribcage and abdominal wall motion indicated that apnoea was of obstructive origin. Hypopnoea was defined as a reduction in oronasal airflow accompanied by reduction in arterial oxyhaemoglobin saturation of more than 4%. The apnoea–hypopnoea index (AHI) was calculated by dividing the total number of apnoeas and hypopnoeas by total sleep time.

CEPHALOMETRY

Lateral cephalometric radiographs were obtained using a standardized procedure. The awake, seated

Table 1 Clinical and cephalometric variables in 30 subjects, comparing the difficult intubation and control groups, and those with and without OSA (mean (SD)). *P<0.05, **P<0.01, ***P < 0.001, difficult intubation *vs* control group, OSA *vs* no OSA. Length, depth and distance are given in cm, area in cm² and angles in °

Variable	Difficult intubation (*n*=15)	Control (*n*=15)	OSA (AHI ≥10) (*n*=10)	No OSA (AHI<10) (*n*=20)
Clinical data				
Mallampati score	3.5 (0.5)	1.4 (0.5)***	3.2 (1.0)	2.1 (1.1)**
Thyromental distance	7.4 (1.3)	8.7 (1.2)**	7.6 (1.3)	8.3 (1.4)
Neck circumference	43.3 (2.7)	41.3 (2.9)	44.1 (2.8)	41.4 (2.6)*
Head extension	32.5 (4.5)	34.3 (3.9)	29.4 (3.3)	35.4 (3.1)***
Cephalometric data				
Skeletal—linear				
Anterior mandibular depth	4.3 (0.3)	3.9 (0.45)**	4.4 (0.2)	4.0 (0.45)**
Posterior mandibular depth	2.6 (0.4)	2.2 (0.3)*	2.6 (0.5)	2.3 (0.3)
Mandibular length	6.6 (0.6)	7.7 (0.8)***	6.8 (0.8)	7.3 (0.9)
Mandibular ramus length	6.2 (0.5)	6.3 (0.3)	6.0 (0.5)	6.3 (0.3)*
Atlanto-occipital distance	0.52 (0.2)	0.67 (0.2)	0.48 (0.09)	0.65 (0.24)*
Mandibulohyoid distance	2.1 (0.6)	1.7 (0.7)	2.2 (0.7)	1.7 (0.7)
Skeletal—angular				
Lower mandibular angle	78.9 (3.4)	76.1 (3.8)*	79.9 (3.6)	76.3 (3.4)*
Craniocervical angle	100.5 (7.2)	100.6 (7.3)	104.2 (5.9)	98.7 (7.1)*
Cervical angle	7.3 (2.9)	3.1 (1.0)***	8.3 (3)	3.7 (1.6)***
Occlusal–goniohyoid angle	51.5 (9.8)	44.1 (9.8)*	57.2 (4.7)	43.1 (9.1)***
Soft tissue				
Total tongue area	29.7 (3.7)	26.8 (4.4)	30.5 (3.5)	27.1 (4.2)*
Soft palate length	4.0 (0.3)	3.7 (0.3)*	4.0 (0.2)	3.8 (0.4)

subject was instructed to maintain natural head position by fixing a distant gaze on an imaginary horizon in order to obtain their customary visual axis.[21] This head position was fixed using a cephalostat. To minimize radiation, exposure was adjusted to maximize definition of the craniofacial and cervical skeletal, and soft tissues on a single radiograph. A radio-opaque marker (10 cm) was placed anteriorly in the midline to correct for magnification (distance from tube to midline 1.51 m; from midline to film 0.16 m). Each exposure was taken at end-expiration with the mouth closed, molars in habitual occlusion and tongue relaxed. Tracings of the radiographs were made on lead acetate paper using standard anthropological and dentofacial landmarks.[28] Measurements were made from these tracings using a calibrated digitizing tablet (Calcomp, Scottsdale, USA) connected to a personal computer. Reference points and measurements made are shown in figure 1.

DATA ANALYSIS

The association of sleep apnoea (defined as AHI ≥10) with difficult intubation was assessed using Fisher's exact test. Clinical, polysomnographic and cephalometric variables were compared between the difficult intubation and control groups and between those with and without sleep apnoea (as defined above) using one-way analysis of variance. P<0.05 was regarded as statistically significant.

Results

There were no significant differences between the difficult intubation and control groups in age (59.8 (range 40–76) and 53.0 (35–68) yr, respectively), height (171.3 (SD 7.0) and 170.5 (9.0) cm), weight (89.0 (13.6) and 83.3 (15.6) kg) or body mass index (30.8 (3.5) and 29 (3.1) kg m^{-2}). There were 13 males and two females in each group.

AHI was significantly greater (P<0.02) in the difficult intubation (28.4 (31.7)) compared with the control group (5.9 (8.9)) (fig. 2). Apnoeas were predominantly obstructive in nature, with the proportion of obstructive or mixed obstructive/central apnoeas being 95.9 (6.4)% in the difficult intubation and 94.8 (10.7)% in the control group. Using an AHI of ≥10 to define OSA, eight of 15 patients in the difficult intubation group had OSA, in five of whom it was severe (AHI >40). Two of 15 control patients had OSA: one mild (AHI=17.4) and the other moderate (AHI=33.4). These differences were significant (P<0.03).

Clinical and cephalometric variables (table 1, fig. 3) were divided into three distinct groups: those showing an association with difficult intubation, those associated with OSA or those associated with both. Those associated with difficult intubation alone included smaller thyromental distance and mandibular length, and greater posterior mandibular depth and soft palate length. Those associated with OSA alone included greater neck circumference, tongue area and craniocervical angle, and smaller head extension, atlanto-occipital distance and mandibular ramus length. Those that were associated with both difficult intubation and OSA included greater Mallampati score, anterior mandibular depth, lower mandibular angle, cervical angle and occlusal–goniohyoid angle (fig. 1). Mandibulohyoid distance was not significantly different in the difficult intubation and control groups and was not related to OSA.

Discussion

The major finding of this study was that difficult tracheal intubation was associated strongly with OSA. Patients presenting with difficult intubation had a greater occurrence and severity of OSA relative to the control group, even though we excluded two patients identified as having a trachea which was difficult to intubate because they were being treated for severe OSA. No one included in the control group had been diagnosed previously with OSA. While the possibility of a relationship between difficult intubation and OSA has been proposed by others,[20 25] it has not previously been studied formally.

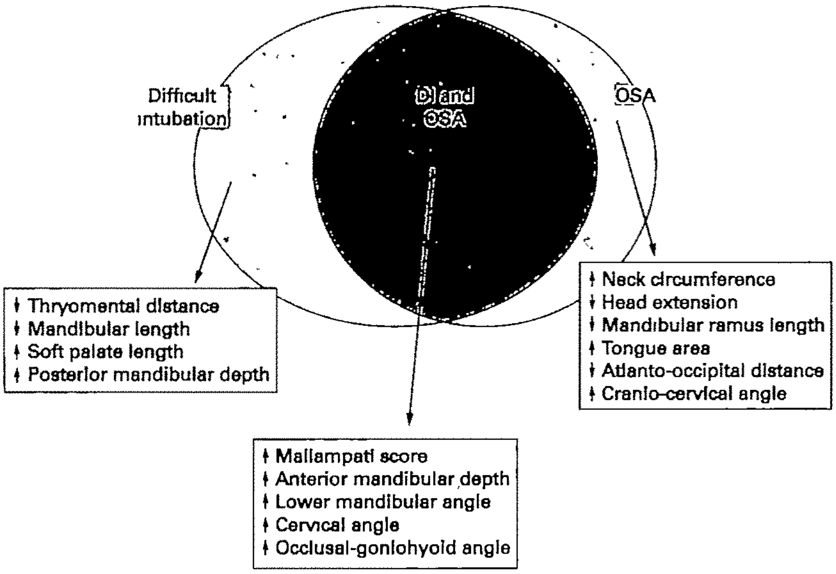

Figure 3 Venn diagram showing unique and shared features of difficult tracheal intubation (DI) and obstructive sleep apnoea (OSA).

This relationship is important because untreated OSA could contribute to morbidity and mortality in the perioperative period and beyond.[6-11] The strength of the relationship appears such that all patients who have a trachea that is difficult to intubate should be regarded as having OSA until excluded by the absence of clinical features (such as snoring, observed apnoeas and excessive daytime sleepiness) and, where doubt exists, sleep studies.[16] Patients in which obvious craniofacial abnormalities were present were excluded from our study, so that predisposition to OSA or difficult intubation was not readily evident from superficial examination.

We examined upper airway characteristics associated with each condition believing that some would be common to both, forming the basis of their relationship, and others would be unique to each, accounting for the incomplete concordance between them.

Most of the skeletal and soft tissue changes which were associated with difficult intubation or OSA, or both, appeared to either decrease the skeletal confines of the tongue or compensate for such a decrease. Factors decreasing skeletal confines included: smaller mandibular length and greater posterior mandibular depth, in the case of difficult intubation alone; smaller mandibular ramus length, in the case of OSA alone; and greater anterior mandibular depth and lower mandibular angle, where both conditions were present. Decreasing the skeletal confines of the tongue acts to decrease the space available for anterior tongue displacement during direct laryngoscopy[29] and to decrease hypopharyngeal dimensions,[30] predisposing to OSA. Our findings are supported by other studies which have demonstrated lower and mid-face elongation in subjects with OSA.[31] The findings are also consistent with studies suggesting that a deeper mandible and greater lower mandibular angle increase intubation difficulty because they diminish mouth opening and necessitate more anterior displacement of the tongue.[12 19] Indeed a greater mandibular angle would increase the degree of posterior relative to downward displacement of the tongue with mouth opening, aggravating both difficulty in tracheal intubation and OSA (when the mouth is open).

The greater cervical angle and, in the case of OSA alone, greater craniocervical angle presumably compensate for this decrease in skeletal confines of the tongue. Their effect would be to increase the distance between the mandible and cervical spine and elongate the tongue and soft tissues of the neck, lifting the hyomandibular complex away from the cervical spine thereby increasing the airway space.[32] This "sniffing the morning breeze" position, with forward inclination of the cervical spine and head extension, may be a wakeful postural compensation for upper airway narrowing. Anaesthetized patients are commonly placed in this position either to facilitate airway maintenance or aid tracheal intubation. Loss of this head posture during sleep with loss of skeletal muscle tone could be an important factor in the pathogenesis of OSA, in addition to the well recognized contribution of sleep-associated loss of pharyngeal muscle tone to upper airway narrowing.

The limited head extension observed with OSA may reflect the fact that the cervical and craniocervical angles are already increased so that the neck is already extended (see above), limiting further extension. This suggested mechanism has not been proposed previously, and is supported by the finding that atlanto-occipital distance is reduced in OSA patients. While we did not find an association between limited neck extension and intubation difficulty in our patients, others have,[19] and the mechanism may be relevant to their findings, particularly as we demonstrated a greater cervical angle in the difficult intubation group.

The greater tongue area found on lateral cephalometry in OSA patients may reflect a true increase in tongue size or a change in tongue geometry consequent on a change in its skeletal confines. Either way, these changes could, together with changes in cervical angulation, contribute to the greater neck circumference observed in association with OSA patients. This finding is consistent with previous observations.[17]

The strong relationship between increased Mallampati scores and both difficult intubation and OSA may have a different basis in each condition. In the difficult intubation group, soft palate length was greater, which would tend to increase Mallampati score. With OSA, mandibular ramus length was less, which would also increase Mallampati score by decreasing the distance between the floor of the mouth and soft palate. The Mallampati score is used widely to predict difficult intubation[18] and should be explored further as a predictor of OSA.

The occlusal–goniohyoid angle (fig. 1) was related strongly to both difficult intubation and OSA. This angle, which has not been described previously, indicates posterior displacement of the larynx relative to the gonion. It is influenced by several factors related to facial morphology, including mandibular depth, length of the ramus, craniocervical angulation and position of the hyoid, which may explain the strength of its association with both conditions. It may be useful in cephalometry as an easily measured overall assessment of mandibular size and angulation.

The association of decreased thyromental distance with difficult intubation is another observation corroborated by the findings of others.[19] Our data suggest that it may be attributable to a combination of smaller mandibular length, greater anterior and posterior mandibular depths, and an increased lower mandibular angle.

It is important to regard conclusions based on the anatomical associations described above cautiously, as they derive from multiple comparisons in the context of a relatively small number of patients. However we offer them as "hypothesis generating" rather than "hypothesis proving" findings. They appear internally consistent, biologically plausible and many are supported by the findings of others. Several potential interactions between the variables have been referred to above, especially the influence of skeletal structure on the disposition of the soft tissues. Further studies are required to confirm these findings and such studies could allow measurements to be selected and equations generated to reliably predict difficult intubation or OSA, or both, from clinical and cephalometric variables.

In summary, this study showed that subjects in whom the trachea was difficult to intubate were at increased risk of OSA. Complex interrelated anatomical changes appear to be responsible for the association. Linear and angular changes in the mandible decrease the space available for air and instrumentation in the oropharynx. Patients with sleep apnoea appear to compensate for this, at least during wakefulness, by increasing craniocervical angulation. This postural compensation may be lost with muscle relaxation during sleep or when under the influence of sedatives, neuromuscular blocking agents or anaesthetic agents. Patients known or predicted to be difficult to intubate should be screened for signs and symptoms of sleep apnoea, with further investigation and treatment arranged where indicated, to minimize the morbidity associated with this condition both in the perioperative period and beyond.

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British Journal of Anaesthesia 1998; **80**: 612–616

In vivo investigation into the effects of haemodilution with hydroxyethyl starch (200/0.5) and normal saline on coagulation†

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Summary

We have investigated the effects of haemodilution with either saline or hydroxyethyl starch (200/0.5) (HES) on blood coagulation in healthy volunteers *in vivo*. Standard haematological tests (packed cell volume (PCV), platelets, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, antithrombin III, bleeding time and platelet aggregation), and thrombelastography (TEG) were performed before and after administration of either 0.9% saline 1000 ml or HES 1000 ml i.v. over a 30-min period. Dilution of PCV and platelet concentrations as a result of volume load were 9% in the saline group and 19% in the HES group. Reductions in fibrinogen (18.6% and 28.8%) and antithrombin III (25.5% and 37.8%) were significantly greater than could be explained by haemodilution alone in both groups. Indices of platelet aggregation were significantly enhanced by saline haemodilution, but not by HES, which inhibited epinephrine-induced aggregation and prolonged bleeding time. TEG in the saline group showed significantly shortened *r* and *k* times (24% and 26%, respectively), and increased α angle (24%) and maximum amplitude (MA, 6%). HES haemodilution decreased MA (11%) but did not affect other TEG variables. We conclude that haemodilution of normal blood exerted a procoagulant effect, possibly by enhancement of thrombin formation. Circulating concentrations of antithrombin III were depleted more than could be explained by haemodilution alone, leading to a hypercoagulable state. This effect was offset by an antiplatelet action of HES, which was not seen with saline. The mechanism is unknown. (*Br. J. Anaesth.* 1998; **80**: 612–616)

Keywords: blood, coagulation; blood, haemodilution; blood, replacement, fluids, i.v.; measurement techniques, thrombelastography

The hydroxyethyl starches are a relatively new, effective group of compounds designed to provide plasma volume expansion but there has been concern about their effects on coagulation. Many of the studies which have examined the effects of colloids on coagulation have used a crystalloid control[1–4] or have failed to allow for crystalloid that the patient may have been given in addition to the colloid, for example in the cardiopulmonary bypass pump prime.[5 6] However, crystalloid solutions may also affect coagulation. In 1959 Tocantins, Carroll and Holburn[7] and Monkhouse[8] reported that moderate haemodilution with crystalloids could enhance coagulability. This was later confirmed by Janvrin, Davies and Greenhalgh[9] and Heather, Jennings and Greenhalgh,[10] and also by our own findings.[11] Popov-Cenic and colleagues[12] reported that enhanced coagulation, ascribed to premedication and anaesthesia *per se*, was offset by i.v. administration of hydroxyethyl starch. In 1975, Vinnazzer and Bergmann[13], in a double-blind study, compared standard tests of coagulation and thrombelastography before and after operation in two groups, one treated with hydroxyethyl starch and the other with isotonic saline in the perioperative period. Their findings showed a postoperative hypercoagulable state in the control (saline) group but non-significant changes in the test (hydroxyethyl starch) group. As their study was performed after operation, it did not demonstrate if these changes in coagulability were already present after infusion of the i.v. fluid, before any surgical stress response occurred which might have influenced coagulation variables further.

Thrombelastography (TEG) is a technique first developed by Hartert in 1948.[14] It had little clinical use for many years until it was re-evaluated in the surgical setting in 1974. Subsequently it was developed further and more recently has been applied and validated in both liver transplantation and cardiac surgery. The TEG pattern is divided into component variables. Reaction time (*r*) is the interval between the start of recording and the time at which the amplitude of the tracing is 2 mm. It reflects the function of the intrinsic clotting pathway. Coagulation time (*r*+*k*) is the time required for the amplitude to reach 20 mm and provides information not only on intrinsic factors but also on platelets and fibrinogen, which are also represented by the clot formation rate (α°). Maximum amplitude (MA) is the greatest amplitude achieved on the TEG and is a measure of clot strength and elasticity, reflecting the properties of platelets and fibrinogen, and also factor XIII.[15]

We conducted an *in vivo* study in volunteers using commonly used tests of coagulation and TEG, to determine the effect of haemodilution with i.v. fluids

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Table 1 Haematological data before and after haemodilution with saline or hydroxyethyl starch (HES) (mean (SD)). PCV=Packed cell volume; PT=prothrombin time; aPTT=activated partial thromboplastin time; Anti. III=antithrombin III, as a percentage of laboratory normalized values. *$P<0.05$, ***$P<0.001$, within-group differences from baseline

	Saline			HES		
	Baseline (*n*=20)	After dilution (*n*=20)	Change	Baseline (*n*=20)	After dilution (*n*=19)	Change
PCV (%)	43.3 (4.7)	39.0 (3.9)***	−4.1 (1.8)	42.5 (3.2)	34.5 (3.3)***	−7.9 (2.1)
Platelets (10^9 litre^{-1})	208.0 (36.5)	188.8 (36.4)	−19.3 (11.4)	215.9 (45.9)	171.7 (33.5)***	−44.3 (22.1)
PT (s)	13.15 (1.07)	13.85 (1.06)***	0.69 (0.54)	13.09 (0.80)	14.55 (1.01)***	1.46 (0.70)
aPTT (s)	33.9 (2.7)	34.7 (2.9)*	0.74 (1.37)	33.2 (2.9)	36.6 (3.6)***	3.4 (2.1)
Fibrinogen (g litre^{-1})	2.65 (0.75)	2.14 (0.55)***	−0.52 (0.30)	2.68 (0.65)	1.90 (0.47)***	−0.78 (0.27)
Anti. III (%)	116.1 (33.7)	80.1 (15.9)***	37.7 (43.4)	108.8 (30.2)	62.8 (16.0)***	45.9 (36.2)

on coagulation. Standard tests of coagulation such as prothrombin time (PT), activated partial thromboplastin time (aPTT) and bleeding time are generally more sensitive in hypocoagulable states than in enhanced coagulation states.[16] TEG provides a visual pattern of functional clotting status and is the most sensitive method of detecting an increase in coagulability.[17] Therefore, we used both methods to examine coagulation.

Subjects and methods

After obtaining approval from the Human Ethics Committee of the University of Cape Town and informed patient consent, we determined the effects on blood coagulation of infusion of 20% of blood volume using either 0.9% saline (saline) or hydroxyethyl starch (200/0.5) (HES) (HAES-steril, Fresenius AG, Germany) in healthy, ASA I volunteers, weighing 55–85 kg, with no pre-existing disease. There were 20 subjects in each group. A financial inducement was offered to each subject. All subjects were tested twice in a cross-over study, with at least 7 days between tests. A 20-gauge cannula was inserted into an antecubital fossa for blood sampling for standard haematological tests (full blood count (FBC), PT, aPTT, platelet aggregometry, and concentrations of fibrinogen and antithrombin III), bleeding time and TEG. Platelet aggregometry was performed on platelet-rich plasma in a platelet aggregometer (Chrono-log, Havertown, Pa). The change in optical density on addition of successive aggregating agents was recorded as a tracing on a chart recorder. Aggregating agents used were adenine diphosphate (ADP) 5, 10 and 100 μmol litre^{-1}, epinephrine 10 μmol litre^{-1} and ristocetin 1.2 mg ml^{-1}. Percentage aggregation was calculated from the recorded sigmoid curve.

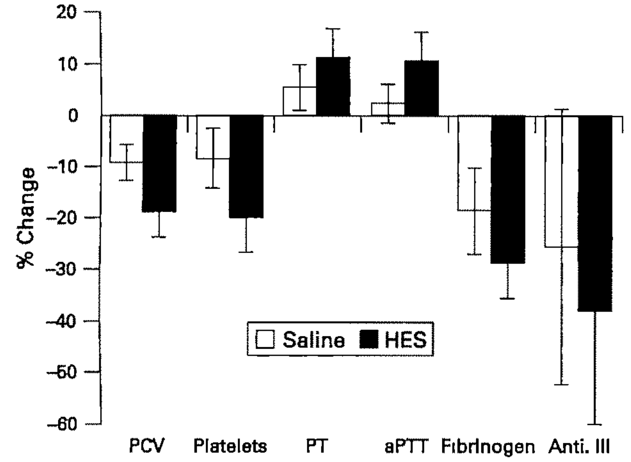

Figure 1 Percentage change from baseline values for haematological variables (mean (SD)) in the HES and control groups. PCV=Packed cell volume, PT=prothrombin time, aPTT=activated partial thromboplastin time and Anti. III=antithrombin III.

Subjects then received either 0.9% saline 1000 ml or colloid 1000 ml (HES) via the cannula. This was infused over 30 min. Provision was made to stop the infusion immediately and exclude any subject who experienced side effects. At the end of infusion, blood was sampled via the cannula, after discarding the first 5 ml, and coagulation studies and TEG were repeated. Disposal of contaminated waste was in accordance with accepted hospital norms.

A separate pilot study was conducted to exclude the method of sampling as a potential source of experimental error. In this study, we showed that sampling from the cannula following infusion of saline, after discarding the first 5 ml, produced the same TEG pattern as a sample obtained simultaneously from a vein on the opposite arm. Therefore, placement of the cannula and the sampling method had no effect on the TEG. We did not study possible effects of HES, but the volume of the cannula (<0.2 ml) and discarded blood (5 ml) implies that any contamination of the subsequent sample was very unlikely.

Table 2 Measures of platelet function (bleeding time and percentage aggregation) before and after haemodilution with saline or hydroxyethyl starch (HES) (mean (SD)). *$P<0.05$, ***$P<0.001$, within-group differences from baseline

	Saline			HES		
	Baseline (*n*=20)	After dilution (*n*=20)	Change	Baseline (*n*=20)	After dilution (*n*=19)	Change
Bleeding time (min)	3.35 (0.89)	3.45 (0.92)	0.1 (0.67)	3.34 (0.8)	4.42 (0 99)***	1 08 (0.45)
ADP 100 μmol litre^{-1}	76.6 (11.1)	79.8 (9.8)*	3.3 (6.1)	72.2 (7.4)	72.3 (10.8)	0.1 (7.1)
ADP 10 μmol litre^{-1}	69.3 (12.8)	72.0 (13.5)	2.5 (8.0)	63.4 (9.9)	62.9 (14.1)	0.6 (7.8)
ADP 5 μmol litre^{-1}	58.5 (17.9)	63.0 (18.5)	4.5 (11.2)	54.0 (13.9)	52.0 (17.3)	2.0 (9.4)
Epinephrine 10 μmol litre^{-1}	53.7 (27.8)	56.0 (31.4)	2.2 (23.9)	58.2 (25.0)	38.4 (29.7)***	19.8 (23.0)
Ristocetin 1.2 mg ml^{-1}	83.4 (8.9)	88.2 (9.9)*	4.7 (9.9)	80.6 (7.2)	82.0 (10.0)	1.5 (8.0)

Table 3 Thrombelastograph data before and after haemodilution with saline or hydroxyethyl starch (HES) (mean (SD)).***$P<0.001$, within-group differences from baseline

	Saline			HES		
	Baseline (n=20)	After dilution (n=20)	Change	Baseline (n=19)	After dilution (n=18)	Change
r time (min)	13.4 (3.5)	10.2 (3.0)***	−3.2 (1.2)	13.1 (3.6)	11.7 (3.6)	−1.4 (4.7)
k time (min)	7.1 (1.8)	5.3 (1.6)***	−1.8 (1.2)	7.1 (2.0)	6.6 (2.2)	−0.5 (2.4)
Alpha angle (°)	37.0 (7.4)	45.7 (9.4)***	8.7 (5.5)	37.8 (7.6)	38.1 (9.4)	0.3 (8.6)
MA (mm)	50.0 (5.4)	53.2 (5.4)***	3.2 (2.4)	50.8 (8.6)	45.0 (6.6)***	−5.8 (6.5)

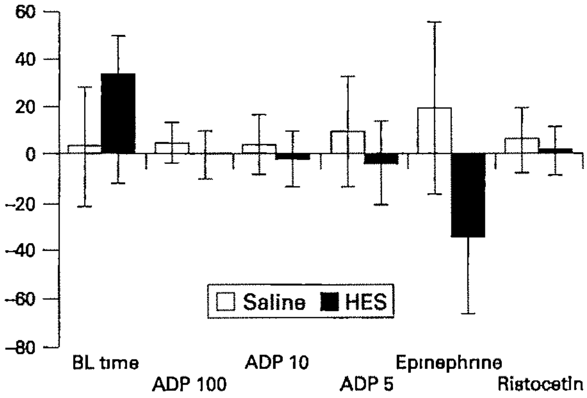

Figure 2 Percentage change from baseline values for measures of platelet function (mean (SD)) in the HES and control groups. BL time=Bleeding time, and ADP 100, 10 and 5=adenosine diphosphate 100, 10 and 5 μmol litre^{-1}, respectively.

Data before and after infusion of fluid in each group were compared using paired t tests. Changes from values before infusion were calculated as numerical data and as percentage change from baseline.

Results

In one subject in the HES group it was impossible to obtain blood samples after infusion without repeat venepuncture, and in another subject there was a technical failure with the TEG, resulting in 18 complete sets of data in the HES group and 20 in the saline group.

Packed cell volume (PCV) was reduced by approximately 19% and 9% of baseline values after infusion of HES and saline, respectively (table 1, fig. 1). Reduction in platelet count was observed in both groups, although in the saline group this was not significantly different from baseline. There were significant increases in PT and aPTT in both groups, but values after dilution were within the normal range quoted by our laboratory for both tests. Concentrations of fibrinogen and antithrombin III decreased in both groups to a greater degree than could be explained by haemodilution alone, and the percentage change in these two variables was significantly greater than the percentage change in PCV ($P<0.001$). The percentage decrease in antithrombin III after haemodilution was not different between groups (fig. 1).

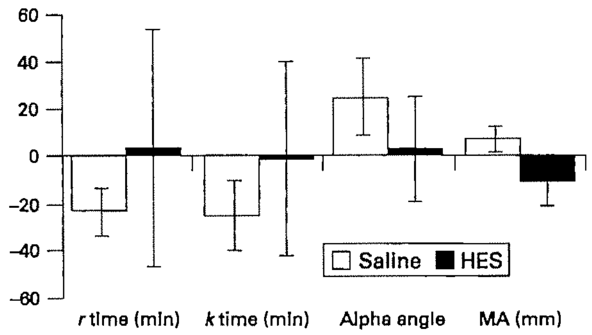

Figure 3 Percentage change from baseline values for TEG data (mean (SD)) in the HES and control groups.

Platelet aggregation, measured by stimulation with ADP 100 μmol litre^{-1} and ristocetin, increased significantly in the saline group. Epinephrine-stimulated platelet aggregation decreased significantly in the HES group (table 2, fig. 2). Bleeding time increased significantly in the HES group.

The TEG results showed significant reductions in r time, k time and MA, and a significant increase in α angle in the saline group, whereas the only change in the HES group was a significant reduction in MA (table 3, fig. 3).

Discussion

Our results demonstrated a predictable decrease (10% and 20%) in PCV and platelet count as a result of haemodilution in the two groups, the greatest decrease being in the colloid group, where presumably less immediate extravascular redistribution of fluid occurs. However, concentrations of antithrombin III decreased significantly to approximately 60% of pre-dilution values in both groups. Concentrations of antithrombin III after dilution were less than half pre-dilution values in some subjects. This suggests that these subjects may have been at a clinically significant increased risk of deep vein thrombosis (DVT) formation if they had been undergoing surgery. The decrease in antithrombin III concentration cannot be explained by dilutional factors alone, especially when considered in conjunction with our TEG results which showed significantly shortened r and k times in the saline group, suggesting enhanced activity of coagulation factors. Monkhouse[8] postulated an imbalance between the formation of thrombin and activity of antithrombins as being responsible for the enhanced coagulation demonstrated after haemodilution.

Our findings suggest that haemodilution *per se* may induce formation of thrombin, with subsequent consumption of both fibrinogen and antithrombin III. The enhanced platelet aggregation observed with some reagents in the crystalloid group after dilution also seems to suggest that i.v. crystalloid induces an increase in coagulability. The absence of a significant increase in platelet aggregation in the colloid (HES) group may be because of the known antiplatelet effect of HES,[18] possibly via a specific effect on von

Willebrand factor,[19] which may balance the hypercoagulability produced by haemodilution. This is supported by our finding of a probable consumption of antithrombin III, together with absence of enhancement of platelet aggregation (in fact, a decrease with one reagent) in this group. The increased α angle and MA in the saline group are in keeping with the enhanced coagulability and platelet aggregation seen in this group.

TEG measures whole blood coagulation, whereas PT and aPTT are measured on platelet-poor plasma. The slight prolongation of PT and aPTT in this study probably reflects dilution of coagulation factors in plasma, whereas shortening of *r* and *k* times could be explained by platelet activation or other cell-mediated effects not seen in studies on cell-depleted plasma.

Recent work has suggested that the procoagulant effect of crystalloid infusions may be clinically relevant during surgery. Ng and Lo[16] reported that during surgical blood loss with crystalloid volume replacement, increased whole blood coagulability was observed, which was related to the degree of haemodilution. Heather, Jennings and Greenhalgh[10] demonstrated that saline-induced enhanced coagulability could be used as a predictor of the risk of formation of DVT, which confirmed the suggestion by Janvrin, Davies and Greenhalgh[9] that there might be a relationship between haemodilution with crystalloid solution and the risk of DVT.

Our study has confirmed previous *in vitro* findings that haemodilution with crystalloid solutions increases the coagulability of blood.[11] The results also confirm the *in vitro* suggestion that hetastarch solutions may have a lesser effect, probably mediated via an antiplatelet action. Our finding of enhanced coagulability has recently been confirmed using 30% haemodilution with crystalloids, but not with colloids in an *in vitro* study.[20] In this study, using pH and calcium-corrected diluents, the authors demonstrated a reduction in *r* and *k* times, and an increase in alpha angle at 30% haemodilution with saline. They found no effect of gelatin on the TEG and showed an increase in *k* time, and decreases in alpha angle and MA with starch. These results are compatible with our findings, given the smaller dilutions used in our study.

The clinical implications of this finding are potentially important. Not only do our results suggest that infusion of crystalloid solutions may increase the risk of thrombotic complications in surgical patients, but they also cast doubt on studies of coagulation using crystalloid haemodilution as a control.[2-6 12]

TEG has been used widely to measure coagulation in clinical anaesthesia.[21] The global, yet overlapping, data that are provided by the TEG, allow more appropriate replacement therapy to be given, in addition to providing a useful test of liver function during the immediate period after cross-clamp in liver transplantation.[22 23]The relationship between TEG and standard laboratory tests of coagulation is positive, with the greatest correlation between *r* time and aPTT.[24-27]

Based on our findings we can speculate that infusion of i.v. fluid (1000 ml) could enhance the formation of thrombin and its consequent binding to antithrombin III, thus reducing concentrations of antithrombin III more than can be explained by haemodilution alone. Furthermore, platelet aggregation appears to be enhanced by infusion of saline, but not by HES. This may have clinical implications for the management of stroke, postoperative DVT, vascular surgery, trauma and coronary artery surgery, where current practice is to use large amounts of crystalloid solution for cardiopulmonary bypass pump prime for patients undergoing cardiac revascularization procedures, an effect which might have an adverse reaction on graft survival and postoperative morbidity and mortality.

This study was a preliminary attempt to investigate if our *in vitro* observations could be confirmed in an *in vivo* situation, but without the confounding factors of anaesthesia and surgery. It should be repeated using various i.v. solutions at different concentrations to determine the range of haemodilution that enhances coagulation before the dilutional effect becomes too great to sustain increased coagulation, and to investigate the degree to which different solutions may affect the formation of thrombin and platelet aggregation. A recent study has demonstrated that 50% haemodilution of blood with HES or with a modified gelatin solution *in vitro* produced shortening of *r* time, indicating enhanced initiation of coagulation even at extreme haemodilution; this effect was not seen with dextran 40 which inhibited all aspects of coagulation.[28]

The mechanism whereby this effect may occur is unknown. However, it is interesting to observe that there may have been a survival benefit for the evolution of such a mechanism. One may speculate that when internal haemodilution occurs after blood loss, enhanced coagulability may prevent further haemorrhage in the wild state, and this could offer a survival benefit.

We conclude that haemodilution *per se* induced a procoagulant state by an unknown mechanism, and that this may be clinically significant. When haemodilution was produced using hydroxyethyl starch, this procoagulant state was partially offset by an antiplatelet effect.

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British Journal of Anaesthesia 1998; **80**: 617–620

Ease of placement of the laryngeal mask during manual in-line neck stabilization

T. ASAI, J. NEIL AND M. STACEY

Summary

We studied 20 patients, in a randomized, cross-over study, to determine if manual in-line stabilization of the head and neck altered the ease of insertion of the laryngeal mask and its correct positioning. After induction of anaesthesia and neuromuscular block, the laryngeal mask was inserted and adequacy of ventilation assessed while the patient's head and neck were placed in the Magill and manual in-line positions, in turn. Ease of insertion of the mask was assessed using a 10-cm visual analogue scale (VAS) and position using a fibreoptic bronchoscope. Time for insertion of the mask was measured. The laryngeal mask was inserted and adequate ventilation obtained at the first attempt in all 20 patients in the Magill position and in 19 of 20 patients in the manual in-line position. Insertion was always more difficult ($P<<0.001$; 95% CI for difference in VAS 20–55 mm) and time for insertion longer ($P<<0.001$; 95% CI for difference 4.9–11.9 s) in the manual in-line position compared with the Magill position. The incidence of a suboptimal position was significantly higher for the manual in-line position (seven patients) than for the Magill position (15 patients) ($P<0.005$). We conclude that in paralysed patients, manual in-line stabilization of the head and neck made insertion of the laryngeal mask and its correct positioning more difficult. (*Br. J. Anaesth.* 1998; **80**: 617–620)

Keywords: equipment, masks anaesthesia; intubation tracheal, difficult; intubation tracheal, technique

The laryngeal mask has a potential role in patients with difficult airways, because it has been used successfully in those in whom tracheal intubation, ventilation via a face mask, or both, have failed.[1 2] However, the success rate of insertion of the laryngeal mask is low when cricoid pressure is applied and the neck is stabilized using the manual in-line method.[3 4]

Cricoid pressure may often impede insertion of the laryngeal mask,[5–7] but it is not clear if insertion is more difficult when the neck is stabilized in the neutral position (without application of cricoid pressure) than when the neck is flexed and the head extended (Magill position).[6 8 9] One study showed that in non-paralysed patients, there was no significant difference in the ease of insertion or correct positioning of the mask between the Magill and manual in-line positions.[8] Another study showed a high success rate of insertion of the laryngeal mask even when a neck collar was applied in paralysed patients.[9] However, we found that in paralysed patients, insertion of the laryngeal mask was sometimes difficult when the patient's head was placed directly on the trolley (without neck stabilization).[6] In none of these studies was the ease or success rate of insertion of the laryngeal mask compared between the Magill and manual in-line positions in *paralysed* patients.

In this study, we determined if manual in-line stabilization of the head and neck altered the ease of insertion of the laryngeal mask and its correct positioning in patients in whom a neuromuscular blocking agent was given.

Patients and methods

We studied 20 patients (ASA I or II) undergoing elective surgery, in whom neuromuscular block was used as part of the anaesthetic procedure. Patients were not included if they had any pathology of the neck, upper respiratory tract or upper alimentary tracts, or were at risk of pulmonary aspiration of gastric contents. Patients with Mallampati class 3 or 4[10 11] were also excluded. The local Research Ethics Committee approved the study and written informed consent was obtained from all patients.

Temazepam 20 mg orally was given as premedication. In the anaesthetic room, an electrocardiograph, pulse oximeter and arterial pressure cuff were attached. After preoxygenation of the patient, anaesthesia was induced with propofol, and neuromuscular block was produced with either vecuronium or atracurium, and was confirmed using a peripheral nerve stimulator. Anaesthesia was maintained with a volatile agent and nitrous oxide in oxygen.

In a randomized, cross-over manner, the laryngeal mask was inserted while the patient's head and neck were placed in the Magill position and the manual in-line position, in turn. The order was randomized by tossing a coin (the Magill position followed by manual in-line position in 11 patients; manual in-line position followed by the Magill position in nine patients). On one occasion, a laryngeal mask was inserted while a pillow was placed under the patient's occiput, the head was extended on the neck and the

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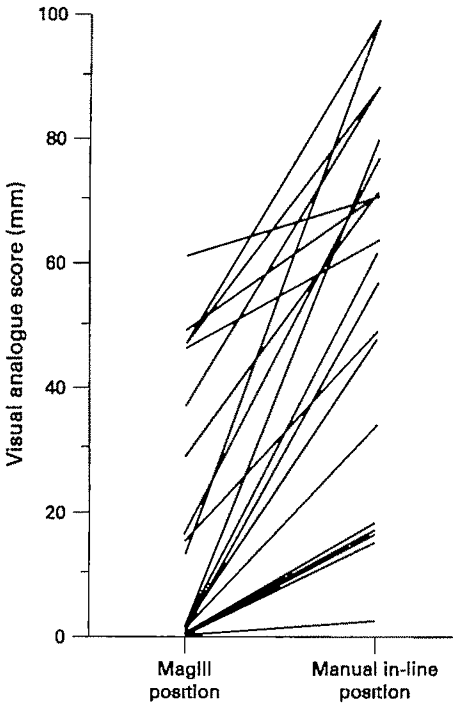

Figure 1 Visual analogue score for ease of insertion of the laryngeal mask while the patient's head and neck were placed in the Magill or manual in-line position. Insertion was significantly easier using the Magill position (P<<0 001).

lower neck flexed, as described by Magill.[12 13] On the other occasion, insertion was attempted after the pillows had been removed and the patient's head and neck were stabilized using the manual in-line method. All insertion attempts were made by the authors (J. N. or M. S.) who were not involved in a previous study.[6] We did not attempt to blind the investigators from patient allocation, as the position of the patient's head and neck and the assistant's hands stabilizing the head and neck were often apparent, even if they were covered by a cloth.

A size 4 mask was used for both males and females unless it was judged that the size 4 was too large; the same size of mask was used on both occasions. The cuff was inflated with the recommended maximum volume of air (20 ml for the size 3 and 30 ml for the size 4) and the breathing system was connected to the laryngeal mask. Ventilation via the laryngeal mask was assessed and considered adequate when the chest expanded with satisfactory compliance during inflations, without an audible gas leak around the mask.

A fibreoptic bronchoscope was passed through the laryngeal mask. The view of the larynx through the bronchoscope with its tip positioned at the level of the grille of the mask was scored:[6] A=the glottis, but not the tip of the epiglottis, seen; B_a=glottis and tip of the epiglottis seen; B_b=epiglottis pressed downward; B_c=epiglottis not pressed downward, but glottis not seen; F=failure of placement. The laryngeal mask was arbitrarily judged as positioned correctly when the score was A.[6]

Table 1 Time (s) for insertion of the laryngeal mask (mean (SD) [range]) while the patient's head and neck were in the Magill or manual in-line position. The difference in times between two positions was significant (P<<0.001)

	Time (s)
Magill position (n=20)	11.7 (4.0) [5–18]
Manual in-line position (n=20)	20.1 (6.6) [10–32]

Table 2 Relative position of the laryngeal mask to the larynx. Category A=the glottis, but not the tip of the epiglottis seen; B_a=glottis and tip of the epiglottis seen; B_b=epiglottis pressed downward; B_c=epiglottis not pressed downward, but glottis not seen; F=failure of placement. The proportion of correct positionings of the mask (category A) was significantly higher with the Magill position than with the manual in-line position (P<0.005)

	Category				
	A	B_a	B_b	B_c	F
Magill position (n=20)	13	6	1	0	0
Manual in-line position (n=20)	5	5	8	1	1

Only one attempt at insertion was allowed for each occasion. Ease of insertion of the laryngeal mask was assessed using a visual analogue scale (VAS) (0–100 mm) for each attempt with the word "easy" on the left side of the line and "difficult" on the right. Time for insertion of the laryngeal mask, between removal of the face mask and connection of the laryngeal mask to the breathing system, was measured.

STATISTICAL ANALYSIS

Normal plots (plots of normal scores) and the Shapiro–Francia W' test showed that the difference in VAS for ease of insertion between the Magill and manual in-line positions was normally distributed; therefore, the paired Student's t test was used to compare ease of insertion. The McNemar test (paired proportion test)[14] was used to compare the proportions of correct placement of the laryngeal mask between the two positions. $P<0.05$ was considered significant. The 95% confidence intervals (CI) for differences between the two positions in (1) VAS, (2) time for insertion and (3) proportion of correct placements of the mask were calculated.

In a preliminary study we found that with the standard insertion method (Magill position), mean VAS for ease of insertion of the mask was 20–30 with an SD value of approximately 20. We estimated that the SD of the difference between the two positions would be up to 30, and considered that a clinically important difference in ease in insertion between the two positions would be 25. Less than 10 patients were required to detect this difference with a power of 0.9.[14] However, to obtain reasonable confidence intervals for differences between the two positions, we studied 20 patients.

Results

SUCCESS RATE AND EASE OF INSERTION

The laryngeal mask was inserted in all patients and adequate ventilation obtained when the patient's head and neck were placed in the Magill position, whereas adequate ventilation was obtained in 19 of 20 patients when the manual in-line position was used. Insertion was always more difficult when the manual in-line position was maintained than when the Magill position was used (P<<0.001; 95% CI for difference in VAS 20–55 mm) (fig. 1). In addition,

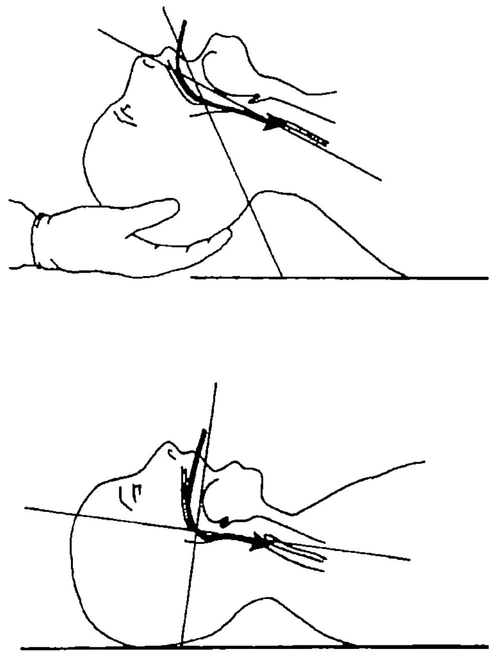

Figure 2 Recommended positioning of the head and neck for insertion of the laryngeal mask (Magill position)[12, 13] (top). Insertion in theory becomes more difficult when the occiput is placed directly on the trolley and manual in-line neck stabilization is used, as the angle between the oral and pharyngeal axes becomes more acute (bottom). Reproduced with modification from Asai,[15] with permission from WB Saunders.

the time taken for insertion was significantly longer in the manual in-line position than in the Magill position ($P<<0.001$; 95% CI for difference 4.9–11.9 s) (table 1).

POSITIONING OF THE LARYNGEAL MASK

Fibrescopy confirmed that the position of the laryngeal mask was correct (score A) in 13 of 20 patients (65%) when the mask was inserted in the Magill position, whereas the position was correct in only five patients (25%) when manual in-line stabilization was used (table 2). In all five patients in whom the position of the mask was correct during manual in-line stabilization, the position was also correct in the Magill position. The incidence of a suboptimal position was significantly greater in the manual in-line position than in the Magill position ($P<0.005$; 95% CI for difference 0.19–0.61).

Discussion

It has been claimed that insertion of the laryngeal mask is best achieved when the neck is flexed and the head extended, as described by Magill ("sniffing position").[12, 15] In theory, insertion may be more difficult when the head and neck are in the neutral position, because the angle between the oral and pharyngeal axes becomes acute at the back of the tongue (fig. 2). Ishimura and colleagues used curved aluminium plates with several different angles as a model for the oropharyngeal structure, and found that it was difficult to advance the laryngeal mask beyond the angle of the plate when the angle was less than 90°.[16]

In our study, the time for insertion of the laryngeal mask was significantly longer when the patient's head and neck were placed in the manual in-line position than in the Magill position. This result is in contrast with that of Brimacombe and Berry who reported that the mask was inserted within 10 s in all 40 patients when the head and neck were placed in the Magill position and in 38 of 40 patients in whom manual in-line stabilization was applied.[8] Although Pennant, Pace and Gajraj did not compare the ease of insertion of the laryngeal mask between the two positions, they reported that time for insertion was 22–87 s (mean 32 s) in patients in whom a Philadelphia collar was applied.[9] This suggests that insertion was moderately difficult in their study.

Gabbott and Sasada found that it was often impossible to ventilate via the laryngeal mask when cricoid pressure and the manual in-line method were applied.[3, 4] Our study and previous studies have shown that it is generally possible to insert and ventilate via the laryngeal mask, even when the patient's head and neck are stabilized.[8, 9] Therefore, it is reasonable to conclude that the main cause of failure in insertion of the laryngeal mask in this circumstance is cricoid pressure.

It has been suggested that in anaesthetized patients who are at risk of pulmonary aspiration and in whom the use of the laryngeal mask is considered to be justifiable, cricoid pressure should be released temporarily during insertion of the mask.[5–7] However, in patients in whom both stabilization of the neck and cricoid pressure are required, time for insertion of the laryngeal mask and thus time for release of cricoid pressure may be unacceptably long.

In summary, we have shown that in paralysed patients, manual in-line stabilization of the patient's head and neck made insertion of the laryngeal mask and its correct positioning more difficult.

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British Journal of Anaesthesia 1998; **80**: 621–627

LABORATORY INVESTIGATIONS

Comparison of the effects of sevoflurane, isoflurane and halothane on rat myocardium

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Summary

The effects of sevoflurane on myocardial contraction and relaxation are poorly understood. Therefore, we studied the effects of equi-anaesthetic concentrations (0.5, 1, 1.5, 2 and 2.5 MAC) of sevoflurane, isoflurane and halothane on inotropic and lusitropic (myocardial relaxation) variables, and post-rest potentiation in rat left ventricular papillary muscles *in vitro*. Sevoflurane and isoflurane caused comparable concentration-dependent negative inotropic effects which were significantly lower than those induced by halothane ($P<0.05$). Sevoflurane and isoflurane did not modify lusitropic variables under low or high load, whereas halothane showed a negative lusitropic effect at high concentrations. Halothane suppressed post-rest potentiation, whereas isoflurane and sevoflurane did not. Post-rest recovery was unaffected by halothane, isoflurane or sevoflurane at any concentration. Thus in rat myocardium, sevoflurane and isoflurane caused comparable negative inotropic effects, had no significant lusitropic effects and did not alter post-rest potentiation, suggesting that they did not significantly modify the functions of the sarcoplasmic reticulum. (*Br. J. Anaesth.* 1998; **80**: 621–627)

Keywords: anaesthetics volatile sevoflurane; anaesthetics volatile isoflurane; anaesthetics volatile halothane; heart myocardial function; heart isolated preparation; rat

Sevoflurane is a volatile halogenated anaesthetic characterized by low blood-gas solubility and lack of pungency. These characteristics enable more rapid induction of anaesthesia, more precise adjustment of its effects, faster recovery and administration by mask.[1] The cardiovascular effects of sevoflurane have been studied *in vivo* in animals[2–4] and humans.[5–7] These studies demonstrated that sevoflurane was less cardiopressant than halothane[7] and that it induced haemodynamic changes comparable with those observed with isoflurane, except that heart rate was generally lower than with isoflurane.[2 3 5 6] Nevertheless, intrinsic myocardial contractility is difficult to assess *in vivo* because variables used to quantify it are not completely independent of heart rate or load, and because anaesthetic agents markedly modify the activity of the autonomic nervous system. More recently, some *in vitro* experiments showed that sevoflurane induced electrophysiological changes comparable with those observed with isoflurane.[8 9] The negative inotropic effect of sevoflurane has been related to inhibition of trans-sarcolemmal calcium flux.[8 10] However, there are no data at present comparing the inotropic effects of sevoflurane, isoflurane and halothane. Furthermore, although volatile anaesthetics may impair myocardial relaxation (lusitropy),[11] the lusitropic effects of sevoflurane have not been studied *in vitro*.

In this study, we have compared the inotropic and lusitropic effects of equi-anaesthetic concentrations of sevoflurane, isoflurane and halothane on isolated rat myocardium. We also compared the effects of these anaesthetics on post-rest potentiation of isometric force which provides a useful method of studying the function of the sarcoplasmic reticulum (SR) in a biochemically intact preparation.

Materials and methods

We studied adult Wistar rats (Iffa Credo, France), weighing 250–300 g, according to the recommendations of the Helsinski Declaration and the regulations of the official edict of the French Ministry of Agriculture.

After brief anaesthesia with ether, the hearts were removed rapidly and left ventricular papillary muscles were excised carefully and suspended vertically in a 200-ml jacketed reservoir with Krebs–Henseleit bicarbonate buffer solution containing (mmol $litre^{-1}$): NaCl 118, KCl 4.7, $MgSO_4$ 1.2, KH_2PO_4 1.1, $NaHCO_3$ 25, $CaCl_2$ 2.5 and glucose 4.5. The Krebs–Henseleit solution was prepared daily with highly purified water (Ecopure, Barnstead/Thermolyne Corporation, Dubuque, IA). The jacketed reservoir was maintained at 29°C with a thermostatic water circulator (Polystat 5HP, Bioblock, Illkirch, France) and continuous monitoring of the temperature of the solution (Pt100 temperature probe, Bioblock). Preparations were field-stimulated at 12 pulses min^{-1} by two platinum electrodes with rectangular wave pulses of 5-ms

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duration just above threshold. The bathing solution was bubbled with 95% oxygen–5% carbon dioxide, resulting in a pH of 7.40. After a 60-min stabilization period at the initial muscle length at the apex of the length-active isometric tension curve (*l*max), papillary muscles recovered their optimal mechanical performance, which remained stable for many hours. Suitable preparations were selected on the basis of the following criteria: length at *l*max ≥3.0 mm, cross-sectional area (CSA) ≤1.20 mm^2, ratio of resting force to total isometric force (RF/TF) ≤0.30 and *R*1 ≤0.85 (*R*1=ratio of isotonic shortening and lengthening velocities at a load equal to preload for *l*max), as reported previously.[12]

Control values for each mechanical variable were recorded. Then, the extracellular calcium concentration ($[Ca^{2+}]_o$) was decreased from 2.5 to 0.5 mmol litre^{-1} as rat myocardial contractility approaches a maximum at 2.5 mmol litre^{-1} and hence it is difficult to quantify inotropic changes without previously decreasing $[Ca^{2+}]_o$.[12] Moreover, a decrease in $[Ca^{2+}]_o$ is necessary to study post-rest potentiation.[12] To ensure that the inotropic reserve was comparable between groups, suitable preparations were selected as follows: the decrease in active isometric force and maximum shortening velocity should be within 40–75% and 60–80% of control values at $[Ca^{2+}]_o$ 2.5 mmol litre^{-1}, respectively. Thereafter, we studied the effects of equi-anaesthetic concentrations (0.5, 1.0, 1.5, 2.0, 2.5 minimum alveolar concentration (MAC)) of halothane (*n*=8), isoflurane (*n*=8) and sevoflurane (*n*=8) on mechanical variables, and on post-rest potentiation.

Halothane (Fluotec 3, Cyprane Ltd, Keighley, UK), isoflurane (Fortec 3, Cyprane Ltd) and sevoflurane (Sevotec 3, Ohmeda, West Yorkshire, UK) were delivered with specific vaporizers using carbogen as the carrier gas. The gas mixture was bubbled continuously in the bathing solution. To minimize evaporation of anaesthetic vapours, the jacketed reservoir was sealed with a thin paraffin sheet (Parafilm M, American National Can, Greenwich, CT, USA), as described previously.[11] Anaesthetic concentrations in the gas phase were measured continuously using an infrared calibrated analyser (Capnomac, Datex, Helsinki, Finland). The MAC values of halothane, isoflurane and sevoflurane in adult rats at 29°C were calculated as 0.6%, 0.8% and 1.44vol%, respectively.[13–15] These concentrations in the gas phase correspond to a concentration of approximately 0.25 mmol litre^{-1} in the bathing solution. The concentrations tested were equivalent to 0.5, 1, 1.5, 2 and 2.5 MAC. A 20-min period of equilibration was allowed between each anaesthetic concentration and recording of mechanical variables.

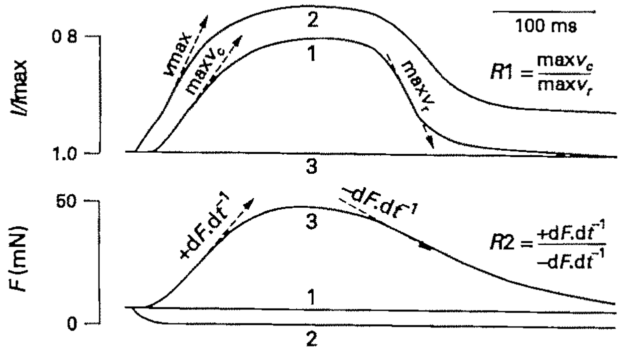

Figure 1 Mechanical variables of contraction and relaxation. Top: muscle shortening length (*l*/*l*max) *vs* time. Bottom: force (*F*) *vs* time. Twitch 1 was loaded with preload only at *l*max. Twitch 2 was loaded with the same preload as twitch 1 but was abruptly clamped to zero load with critical damping just after electrical stimulus. Twitch 3 was fully isometric.

Table 1 Control values (mean (SD)) of the main mechanical variables in papillary muscle strips. *v*max=Maximum unloaded shortening velocity; AF=acting force per cross-sectional area; *R*1=contraction–relaxation coupling variable under low load; *R*2=contraction–relaxation variable under high load. No significant differences between groups

	Halothane group (*n*=8)	Isoflurane group (*n*=8)	Sevoflurane group (*n*=8)
*v*max (*l*max s^{-1})	2.26 (0.48)	2.15 (0.28)	1.93 (0.30)
AF (mN mm^{-2})	40 (10)	42 (16)	34 (16)
*R*1	0.63 (0.12)	0.70 (0.10)	0.72 (0.19)
*R*2	1.77 (0.22)	1.77 (0.16)	1.61 (0 12)

ELECTROMAGNETIC LEVER SYSTEM AND RECORDING

The electromagnetic lever system has been described previously.[11] [12] Briefly, the load applied to the muscle was determined using a servo mechanism-controlled current through the coil of an electromagnet. Muscular shortening induced displacement of the lever, which modulated the light intensity of a photoelectric transducer. All analyses were made from digital records of force and length obtained with a computer, as described previously.[11] [12]

MECHANICAL VARIABLES

Conventional mechanical variables at *l*max were calculated from three twitches. The first twitch was isotonic and was loaded with the preload corresponding to *l*max. The second twitch was abruptly clamped to zero load just after the electrical stimulus; the muscle was released from preload to zero load with critical damping in order to slow the first and rapid shortening overshoot resulting from the recoil of series passive elastic components, as reported previously[16]; the maximum unloaded shortening velocity (*v*max) was determined from this twitch. The third twitch was fully isometric at *l*max.

The mechanical variables characterizing the contraction and relaxation phases, and the coupling between contraction and relaxation are defined below (fig. 1).

Contraction phase

We determined *v*max using the zero load clamp technique; maximum shortening velocity (maxv_c) of the twitch with preload only; maximum isometric active force normalized per cross-sectional area (AF); and peak of the positive force derivative normalized per cross-sectional area (+d*F*.dt^{-1}). *v*max and AF tested the inotropic state under low and high loads, respectively.

Relaxation phase

We determined maximum lengthening velocity of the twitch with preload only (maxv_r) and the peak of the negative force derivative at *l*max normalized per

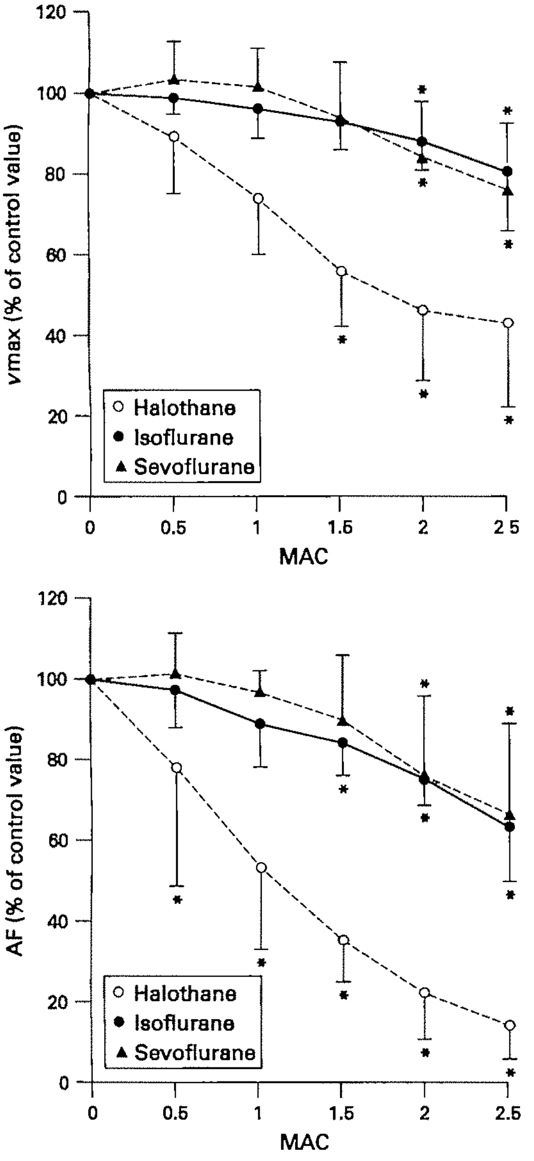

Figure 2 Effects of halothane, isoflurane and sevoflurane on maximum unloaded shortening velocity (*v*max) and maximum isometric active force normalized per cross-sectional area (AF). Data are mean (SD). *$P<0.05$ *vs* control values.

cross-sectional area ($-dF.dt^{-1}$). These two variables describe the relaxation phase under low- and high-loading conditions, respectively. However, as changes in the contraction phase induce coordinated changes in the relaxation phase,[11 12] maxv_r and $-dF.dt^{-1}$ could not assess myocardial lusitropy. Thus variations in contraction and relaxation must be considered simultaneously to quantify drug-induced changes in myocardial lusitropy. Therefore, indexes of contraction–relaxation coupling have been developed.[17]

Contraction–relaxation coupling

Coefficient *R*1 (=maxv_c/maxv_r) describes the coupling between contraction and relaxation under low load and thus reflects myocardial lusitropy in a manner which is independent of inotropic changes. In contrast with both maxv_c and maxv_r, *R*1 is not significantly modified by major inotropic changes.[11] Under isotonic conditions the amplitude of sarcomere shortening is greater than that observed under isometric conditions.[18] Because of the lower sensitivity of myofilament for calcium when cardiac muscle is markedly shortened under low load, relaxation proceeds more rapidly than contraction, apparently because of rapid uptake of calcium by the SR. Thus, in rat myocardium, *R*l describes the SR uptake function. Coefficient *R*2 ($=+dF.dt^{-1}/-dF.dt^{-1}$) describes the coupling between contraction and relaxation under high load and thus the lusitropic state under high load in a manner which is less dependent on inotropic changes.[11] When the muscle contracts isometrically, sarcomeres shorten very little.[18] Because of the higher sensitivity of myofilament for calcium,[19] the relaxation time course is determined by calcium unbinding from troponin C rather than by calcium sequestration by the SR. Thus, *R*2 (contraction–relaxation coupling under heavy load) indirectly reflects myofilament calcium sensitivity.[11 17] The contraction–relaxation coupling variables *R*1 and *R*2 have been validated recently as indexes of myocardial lusitropy.[20]

POST-REST POTENTIATION

Recovery of a stable, reproducible isometric contraction after a rest interval (1 min) was studied to identify the effects of volatile anaesthetics on SR function. In the rat, at rest, SR accumulates calcium in addition to that accumulated under regular stimulation, and the force of the first beat after the rest interval (B1) is greater than that of the last beat before the rest interval (B0). In rat heart muscle, post-rest potentiation is highly dependent on SR calcium release.[21] During stimulation of post-rest recovery (B1, B2, B3...), the SR-dependent portion of the activator calcium decreases somewhat towards steady state, which is reached in a few beats. Therefore, comparison of the effects of halothane, isoflurane and sevoflurane on post-rest-potentiated contraction may provide insight into the differential effects of volatile anaesthetics on SR function in a biochemically intact preparation. As described previously, maximal AF during post-rest recovery was studied at $[Ca^{2+}]_o$ 0.5 mmol $litre^{-1}$, after a rest period of 1-min and at a stimulation frequency of 12 pulses min^{-1}.[12] The rate constant, τ, of the exponential decay of AF was determined, as described previously.[12] τ is the number of beats required for post-rest contraction to decay to one-tenth of its maximum (B1); it is assumed to represent the time required for the SR to reset itself, and was therefore used to test SR function.[22]

At the end of the study, muscle cross-sectional area was calculated from the length and weight of papillary muscle, assuming a density of 1. Shortening and lengthening velocities were expressed in *l*max s^{-1}, force in mN mm^{-2} and force derivative in mN mm^{-2} s^{-1}.

STATISTICAL ANALYSIS

Data are expressed as mean (SD). Control values between groups were compared by analysis of variance. Comparison of several means was performed using analysis of variance and Newman–Keuls test. Beat-to-beat decay of active isometric force during post-rest recovery was plotted against the number of beats and fitted to an exponential curve, and regression was performed using the least squares method, as described previously.[12] All *P*

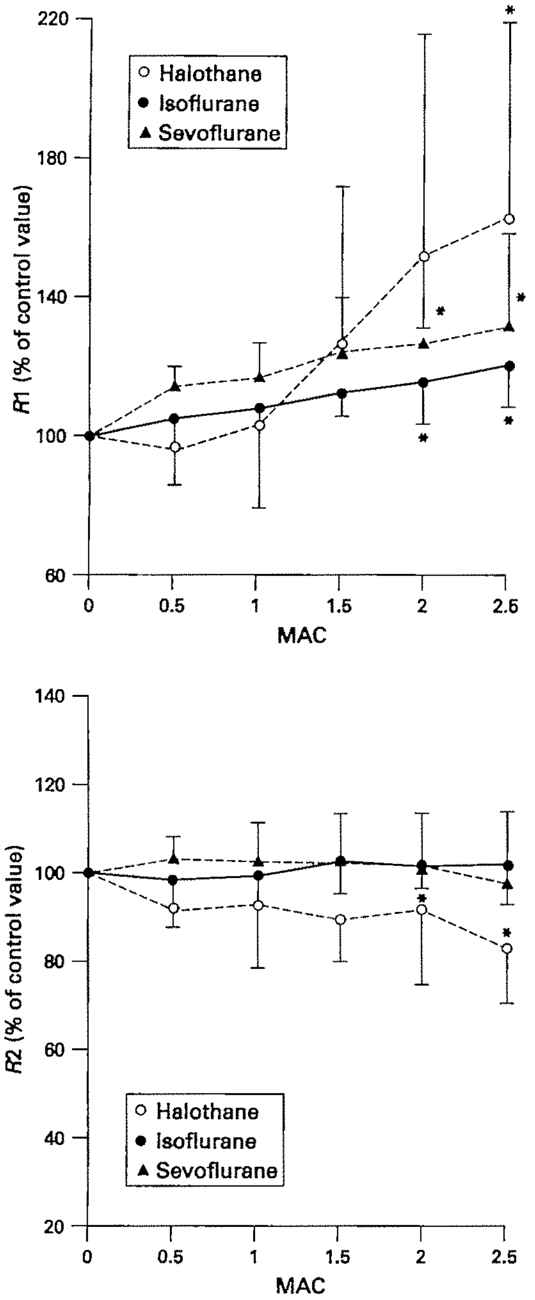

Figure 3 Effects of halothane, isoflurane and sevoflurane on lusitropic variables under low load (*R*1) or high load (*R*2), in the presence of $[Ca^{2+}]_0$ 0.5 mmol litre^{-1}. Data are mean (SD). $*P<0.05$ *vs* control values.

values were two-tailed, and $P<0.05$ was required to reject the null hypothesis. Statistical analysis was performed on a computer using NCSS 6.0 software (Statistical Solutions Ltd, Cork, Ireland).

Results

We studied 24 left ventricular papillary muscles. There were no significant differences in control values for *l*max, CSA, RF/TF or contraction–relaxation coupling under low load (*R*1) at $[Ca^{2+}]_0$ 2.5 mmol litre^{-1} between groups. Mean values for these variables were as follows: *l*max 4.9 (1.3) mm; CSA 0.70 (0.05) mm^2; RF/TF 0.11 (0.05); and *R*1 0.68 (0.08). A decrease in contractility was observed as $[Ca^{2+}]_0$ was decreased: *v*max and AF were 75 (11) % and 50 (11) % of the value at $[Ca^{2+}]_0$ 2.5 mmol litre^{-1}, respectively. These results were consistent with previous reports.[11 12] The control values of the main mechanical variables of papillary muscles in each group are reported in table 1.

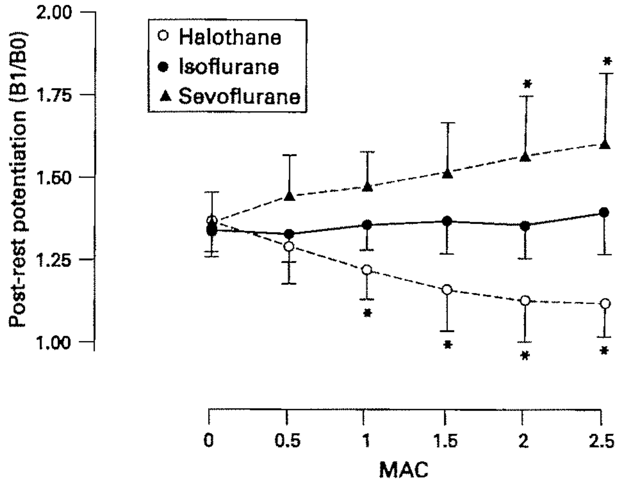

Figure 4 Effects of halothane, isoflurane and sevoflurane on post-rest potentiation. B1=first isometric contraction after rest, B0=last isometric contraction before rest. Data are mean (SD) $*P<0.05$ *vs* control values.

INOTROPIC EFFECTS

Halothane, isoflurane and sevoflurane caused concentration-dependent negative inotropic effects, as shown by the decrease in *v*max and AF (fig. 2). Halothane was the more potent negative inotropic agent, whereas isoflurane and sevoflurane induced comparable negative inotropic effects (fig. 2). The maximum decrease in AF (15 (9) % of control values) measured at 2.5 MAC of halothane was significantly different from that measured at 2.5 MAC of isoflurane and sevoflurane (64 (14) % and 67 (22) % of control values, respectively).

LUSITROPIC EFFECTS

Halothane at 2.5 MAC significantly increased *R*1, indicating a negative lusitropic effect under low load (161 (57) % of control values; $P<0.05$) (fig. 3). Halothane induced a slight concentration-dependent decrease in *R*2. However, it should be noted that the magnitude of this effect was equivalent to that observed by decreasing $[Ca^{2+}]_0$ from 0.50 to 0.25 mmol litre^{-1} (89 (6) % of control values; ns).[11] Isoflurane and sevoflurane induced a slight comparable increase in *R*1 (fig. 3). Isoflurane and sevoflurane did not significantly modify *R*2 at any concentration (fig. 3).

EFFECTS ON POST-REST POTENTIATION AND RECOVERY

Post-rest potentiation (B1/B0) of AF did not differ between groups (137 (10) % in the halothane group, 134 (6) % in the isoflurane group and 136 (10) % in the sevoflurane group). Halothane induced a dose-dependent decrease in post-rest potentiation (fig. 4). At 2.5 MAC, AF developed by the first contraction after the rest period was only 111(10)% of AF developed before the rest period. Isoflurane did not significantly modify post-rest potentiation of AF at any concentration (fig. 4). Sevoflurane increased post-rest potentiation in a concentration-dependent

Table 2 Values (mean (SD)) for the rate constant (τ) of the exponential decay in active isometric force (AF) after post-rest potentiation. τ=number of beats required for post-rest contraction to decay to one-tenth of its maximum (B1). No significant differences between groups

	Halothane group (*n*=8)	Isoflurane group (*n*=8)	Sevoflurane group (*n*=8)
Control	3.1 (0.7)	3.3 (0.5)	3.3 (0.6)
0.5 MAC	3.1 (0.3)	3.0 (0.5)	3.4 (0.6)
1 MAC	3.1 (0.4)	3.2 (0.6)	3.3 (0.7)
1.5 MAC	3.4 (0.7)	3.5 (0.6)	3.4 (0.7)
2 MAC	3.7 (0.4)	3.5 (0.5)	3.3 (0.7)
2.5 MAC	3.9 (1.6)	3.6 (0.3)	3.4 (0.8)

manner (fig. 4). Halothane, isoflurane and sevoflurane did not modify post-rest recovery, as assessed by τ, at any concentration (table 2).

Discussion

We have compared the direct myocardial effects of a wide range of equi-anaesthetic concentrations of sevoflurane, isoflurane and halothane. We showed that, in isolated rat myocardium, the negative inotropic effects of sevoflurane and isoflurane were comparable and significantly lower than those caused by halothane. Whereas halothane induced a marked negative lusitropic effect under low load, sevoflurane and isoflurane did not. In addition, sevoflurane and isoflurane did not alter post-rest potentiation, suggesting that they had no significant effects on SR function.

The cardiovascular effects of sevoflurane were first studied *in vivo* in pigs by Manohar and Parks in 1984.[4] These authors reported a dose-dependent decrease in cardiac output and mean arterial pressure, without significant changes in heart rate. Sevoflurane and isoflurane caused almost comparable *in vivo* effects on systemic and regional haemodynamic variables in rats[3] and dogs.[2] However, these studies did not assess intrinsic myocardial contractility. Harkin and colleagues[23] studied the inotropic effects of several concentrations of sevoflurane in chronically instrumented dogs. However, sevoflurane was studied alone, and variables used to assess myocardial contractility were not completely independent of preload, afterload or heart rate. Moreover, the effects of sevoflurane on autonomic nervous system activity could not be excluded completely. Two clinical studies comparing the cardiovascular effects of isoflurane and sevoflurane in healthy patients or volunteers concluded that isoflurane or sevoflurane anaesthesia induced similar cardiovascular effects. However, these studies may suffer from the same criticisms concerning the relationship between haemodynamic variables and myocardial inotropic or lusitropic state.[5 6] Recently, an *in vitro* study compared the effects of equimolar concentrations of sevoflurane and isoflurane on isolated spontaneous beating guinea pig hearts.[9] Although this study showed that sevoflurane and isoflurane produced equivalent chronotropic and coronary vasodilatory effects, it should be noted that heart rate was not maintained constant, and left ventricular pressure is not considered a good index of the inotropic status of the myocardium.

Our study demonstrated that sevoflurane and isoflurane induced an equivalent concentration-dependent negative inotropic effect (fig. 2). Halothane caused a greater decrease in *v*max and AF than isoflurane or sevoflurane (fig. 2). When MAC values are corrected according to temperature, the negative inotropic effects of halothane and isoflurane that we observed corresponded to those reported previously.[24] The main mechanisms by which volatile anaesthetics cause myocardial depression are profound alteration of the main cellular components involved in intracellular calcium homeostasis. The differences in myocardial depressant effects of volatile anaesthetics, mainly halothane and isoflurane, may be explained by their differential effects on calcium inward currents (I_{Ca}) and SR function.[25 26] In isolated myocytes, sevoflurane decreased the plateau and shortened the duration of the action potential mainly by inhibition of I_{Ca}, presumably via L-type Ca^{2+} channels.[10] Furthermore, Hirota and colleagues[27] suggested that sevoflurane and isoflurane reduced the time constant of Ca^{2+} current inactivation by enhancing the probability of closing the inactivation gate. In isolated rat cardiac cell suspensions, halothane, but not isoflurane, depleted the SR of Ca^{2+}.[26] This effect may be related to the fact that clinically relevant concentrations of halothane, but not isoflurane, gate the cardiac SR Ca^{2+} release channel into the open state.[28] The effects of sevoflurane on SR function are unknown at present, but it could be suggested, based on their equivalent inotropic and lusitropic effects, that they may be similar to those of isoflurane.

It has been shown that in rat myocardium the SR accounts almost entirely for calcium removal from the cytoplasm during the relaxation phase.[29] *R*1 describes the lusitropic state under low load and reflects rapid uptake of calcium by the SR.[11 12] We showed that the increase in *R*1 caused by halothane was greater than those caused by sevoflurane and isoflurane (fig. 3). Our results on the negative lusitropic effects of halothane under low load are in agreement with those reported previously *in vitro*.[30] The lack of negative lusitropic effects of isoflurane and sevoflurane under low load was observed even at high anaesthetic concentrations and agrees with a previous study in chronically instrumented dogs.[31] However, our results suggest that sevoflurane did not significantly modify calcium uptake by the SR.

We showed that halothane decreased post-rest potentiation, whereas isoflurane and sevoflurane did not (fig. 4). This is in agreement with our knowledge of the effects of halothane on SR function. It has been shown that halothane inhibits SR calcium uptake and release and depletes the SR of calcium.[27] Although isoflurane may inhibit cardiac Ca^{2+} ATPase, it did not alter SR calcium content and release. Hence, post-rest potentiation provides a useful tool for examining complex underlying cellular processes, such as SR calcium release in intact cardiac muscle. Sevoflurane caused a slight increase in post-rest potentiation. This effect requires further study to elucidate the precise underlying cellular processes. Two hypotheses can be raised: first, sevoflurane increases the amount of calcium slowly accumulated in the SR during the rest period, and second, it increases calcium release from the SR. Halothane, isoflurane and sevoflurane did not affect post-rest recovery, assessed by the rate constant, τ, of the exponential decay of AF (table 2). This suggests that halogenated anaesthetics do not significantly alter the recirculation fraction of calcium within the SR.[22]

*R*2 tested the lusitropic state under high load and thus could indirectly reflect myofilament calcium sensitivity. Our results showed that sevoflurane and isoflurane did not significantly modify *R*2 (fig. 3), suggesting that they did not induce a lusitropic effect under high load and therefore did not modify myofilament calcium sensitivity. High concentrations of halothane cause a slight decrease in *R*2 but this was not greater than that observed by decreasing calcium to obtain a comparable negative inotropic effect.[11] Indeed, calcium *per se* modulates myofilament calcium sensitivity, according to the cooperativity concept.[32] These results may be clinically important as diastolic function significantly influences overall cardiac performance. Indeed, our results suggest that sevoflurane, at clinically relevant concentrations, does not significantly modify myocardial relaxation.

The following points must be considered in the assessment of the clinical relevance of our results. First, as this study was conducted *in vitro*, it dealt only with intrinsic myocardial contractility and did not take into account the vasodilatory effects of volatile anaesthetics or their influences on sympathetic nervous system tone *in vivo*. Second, this study was carried out at 29°C and at a low-stimulation frequency; however, papillary muscles must be studied at this temperature because the stability of mechanical variables is low at 37°C, and at a low frequency because high-stimulation frequency may induce core hypoxia.[33] Third, it was performed on rat myocardium, which differs from human myocardium. In rat myocardium, contractility is high, calcium-induced calcium release from the SR is highly developed and myosin isoforms are predominantly of the V1 type. Nevertheless, the effects of volatile anaesthetics on the myocardium appear to be similar from one species to another.[23 24]

In summary, in isolated rat myocardium, sevoflurane caused a moderate negative inotropic effect equivalent to that of isoflurane and lower than that of halothane. In contrast with halothane, sevoflurane and isoflurane had no significant lusitropic effects and did not modify post-rest potentiation or recovery, suggesting that they did not significantly alter SR function.

Acknowledgements

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British Journal of Anaesthesia 1998; **80**: 628–633

Effect of xenon on central nervous system electrical activity during sevoflurane anaesthesia in cats: comparison with nitrous oxide

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Summary

We have compared the effects of xenon and nitrous oxide on central nervous system (CNS) electrical activity during sevoflurane anaesthesia in cats by recording the electroencephalogram (EEG), multi-unit activity of the midbrain reticular formation (R-MUA) and somatosensory evoked potentials (SEP). Basal anaesthesia with 2% and 5% sevoflurane was used. With 2% sevoflurane, 70% xenon initially produced rhythmic slow waves which were followed by bursts of high-amplitude sharp waves interrupted by low amplitude slow waves on the EEG. Xenon induced an initial increase, followed by a decrease in R-MUA. Nitrous oxide 70% decreased the amplitude of the EEG activity which was associated with an increase in R-MUA. Xenon suppressed the amplitude of both the initial positive and negative deflections of the SEP to a greater extent than nitrous oxide. With 5% sevoflurane anaesthesia, both anaesthetics increased the frequency of spikes on the EEG and facilitated R-MUA. These findings indicate that xenon has a stimulatory action on CNS background activity and a suppressive action on CNS reactive capability which is more potent than that of nitrous oxide. (*Br. J. Anaesth.* 1998; **80**: 628–633)

Keywords: anaesthetics volatile sevoflurane; anaesthetics gases xenon; anaesthetics gases nitrous oxide; monitoring electroencephalography; monitoring evoked potentials; cat

Xenon is an inert gas that has anaesthetic properties.[1] Its minimum anaesthetic alveolar concentration (MAC) is approximately 71% in humans,[2] that is, more potent than nitrous oxide. Induction of and emergence from xenon anaesthesia are rapid because of its low blood-gas partition coefficient (0.14).[3] It is non-explosive, non-toxic, unreactive and does not undergo biotransformation. Despite such advantages, until now it has not been used in clinical practice because of its expense. However, a decrease in its cost and the availability of a closed anaesthetic breathing system have recently rekindled interest in xenon.[4]

Xenon may be used as an alternative to nitrous oxide. In addition to the anaesthetic actions of nitrous oxide, a stimulatory action on the central nervous system (CNS) has been identified.[5–7] In this study, we compared the actions of xenon on the CNS with those of nitrous oxide by monitoring the electroencephalogram (EEG), reticular multi-unit activity (R-MUA) and somatosensory evoked potentials (SEP).

Materials and methods

We studied nine cats of both sexes, weighing 2.1–4.5 kg, after obtaining approval from our Institutional Committee on Animal Research.

PLACEMENT OF ELECTRODES

The animals were anaesthetized with 5% sevoflurane in oxygen in a small anaesthesia box (40×40×35 cm). A hind limb vein was cannulated and pentobarbital 5–10 mg kg^{-1} was injected i.v. Sevoflurane was then discontinued and the surgical procedures were performed under i.v. pentobarbital anaesthesia (total dose of pentobarbital used was 40 mg kg^{-1}). The animals were placed on a stereotaxic apparatus, and electrodes were implanted over the frontal sinus, parietal cortex, occipital cortex, amygdala (A:12, L:11, D:-6), dorsal hippocampus (A:2, L:9, D:9) and midbrain reticular formation (A:2, L:±3, D:−2), according to the atlas of Snider and Niemer.[8] The parietal cortex electrode in the right side was placed over the sensorimotor cortex (posterior sigmoid gyrus) for recording of SEP. For the cortical surface electrodes, we drilled the bone so as to reach, but not penetrate, the dura. For the depth electrodes, we made the same hole and punctured the dura using an 18-gauge needle. The cortical electrodes were made of stainless steel screws, 2 mm in diameter. The subcortical electrodes were made of side-by-side stainless steel wires, 0.2 mm in diameter, insulated with epoxyresin, except for the cut-end tips. The distance between the tips was 0.5–1.0 mm. Electrode position in the limbic structures was determined by monitoring EEG activity: the electrodes were advanced in 1-mm steps until seizure activity appeared on the EEG.[9] Such seizure activity is induced by injury and

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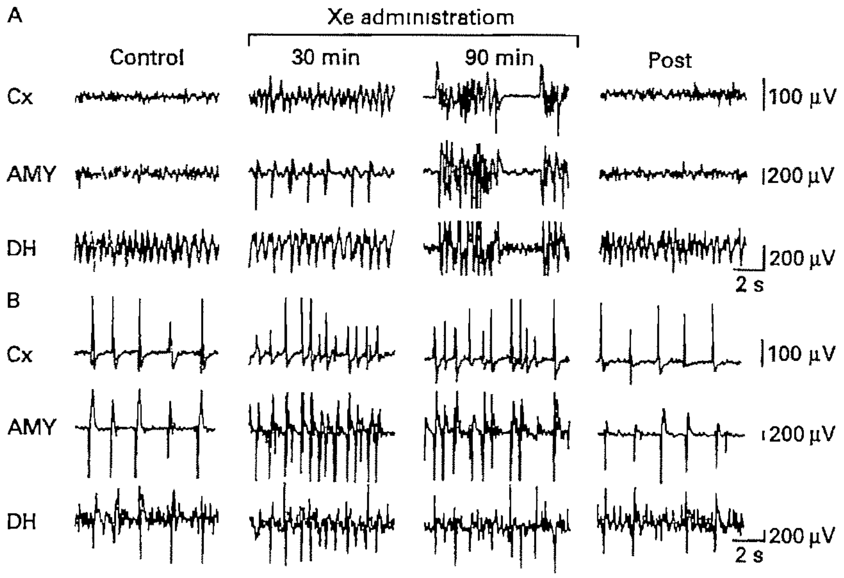

Figure 1 Typical recordings of changes in the electroencephalogram (EEG) during administration of 70% xenon (Xe) in a cat anaesthetized with 2% sevoflurane (A) or 5% sevoflurane (B). Cx=Parietal cortex; AMY=amygdala; DH=dorsal hippocampus.

is typical of the limbic structures. All leads were connected to a miniature vacuum tube socket, which was fixed to the skull with dental cement.

After implantation of the electrodes, the animals were kept in an observation box. On the following day they were moved to a temperature-controlled (23°C) environment, on a 12-h light–dark cycle (lights on 08:00–20:00 h) and were fed food and water *ad libitum*.

RECORDING OF CNS ELECTRICAL ACTIVITY

For cortical EEG recording, the frontal sinus electrode was used as a reference. Depth EEG was recorded using bipolar electrodes. The time constant was set at 0.1 s and the high-cut filter at 100 Hz. R-MUA was obtained differentially between the two active points of the electrodes, amplified (1205C, San-ei, Tokyo) and sent to a high frequency band-pass filter. The high-frequency activity was rectified and smoothed with an electric circuit (envelope detector), using a smoothing time constant of 50 ms. It was expressed as the oscillation of DC voltage: the higher the DC level, the greater the firing of a population of units. The noise level of the recording was estimated by the DC level obtained by inserting a 10-kΩ resistor and a short across the input in place of the animal.[5 7 9 10] In conscious animals, the signal to noise ratio exceeded 10 in all cases. Amplified signals of the EEG and the DC voltage of the R-MUA were fed into a computer via an analogue-to-digital converter (Mac Lab/8s, AD Instruments, Castle Hill, Australia) and stored on hard disk.[11]

On the SEP recording, two dermal needles were placed 1 cm apart, subcutaneously, near the radial nerve of the forepaw that was contralateral to the SEP recording site. A single square wave pulse of 0.5 ms duration with supramaximal intensity required to produce maximal amplitude in the SEP (approximately 10 V) was delivered every 3 s by an electrical stimulator (3F46, NEC San-ei) via an isolator (5384, NEC San-ei). Electrical activity of the parietal cortex

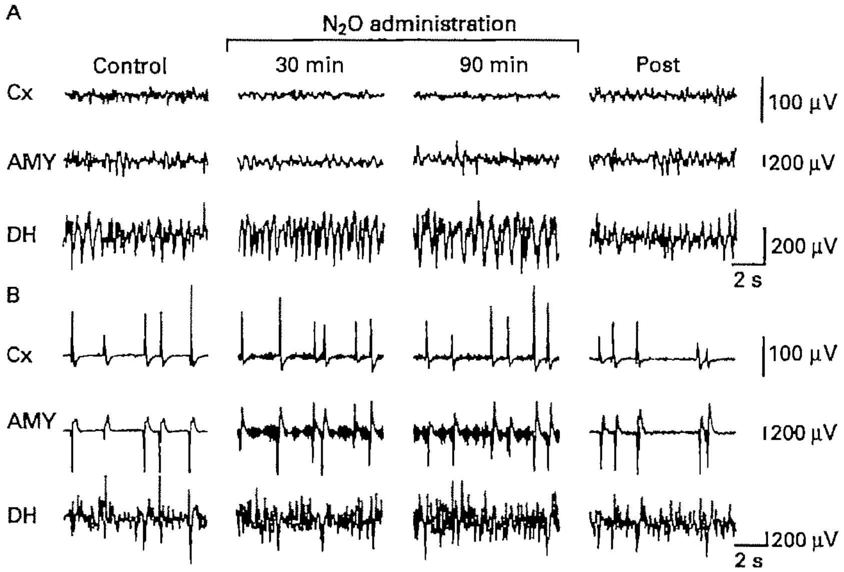

Figure 2 Typical recordings of changes in the EEG during administration of 70% nitrous oxide (N_2O) in the same cat as in figure 1, anaesthetized with 2% sevoflurane (A) or 5% sevoflurane (B). Cx=Parietal cortex, AMY=amygdala; DH=dorsal hippocampus

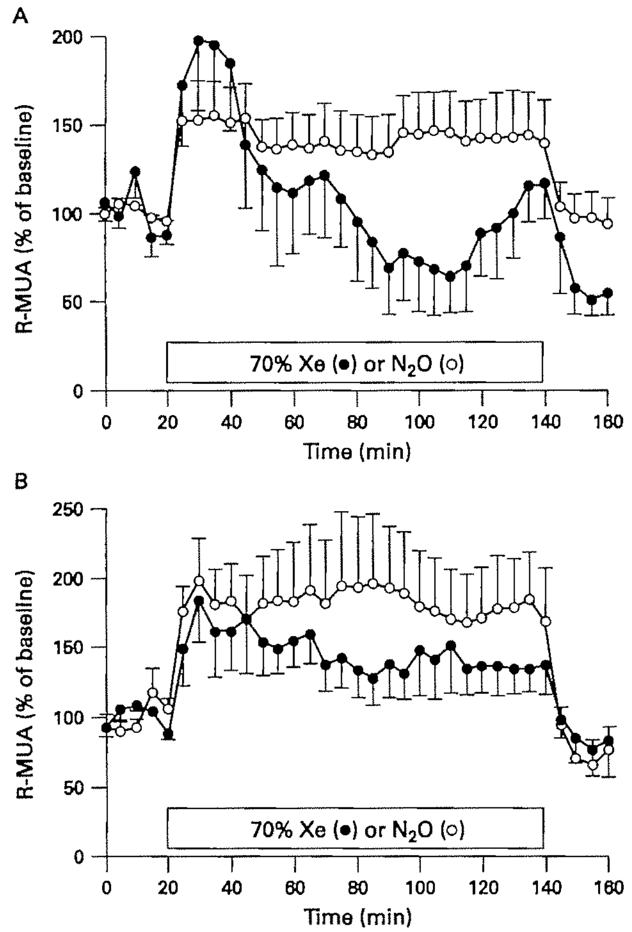

Figure 3 Effects of 70% xenon (Xe) (n=6) or 70% nitrous oxide (N_2O) (n=6) on midbrain reticular multi-unit activity (R-MUA) in cats anaesthetized with 2% (A) or 5% (B) sevoflurane. R-MUA is expressed as mean (SEM) percentage of baseline before xenon or nitrous oxide administration.

electrode was transferred through an AC amplifier (1253A, NEC San-ei, Tokyo) with the time constant set at 0.1 s and high cut-off filter to a computer (Macintosh LC575, Apple, Cupertino, CA, USA), using an analogue-to-digital converter (Mac Lab/8s, AD Instruments, Castle Hill, Australia). Evoked potentials were averaged by 10 trials using a computer program (Scope, AD instruments, Castle Hill, Australia) and stored on hard disk.[12]

EXPERIMENTAL PROCEDURES

At least 4 weeks after implantation of electrodes, the effects of xenon or nitrous oxide on CNS electrical activity were studied. For EEG and R-MUA recordings, administration of xenon or nitrous oxide was performed on different days. For SEP recording, both agents were administered successively in a random sequence on the same day. An interval of at least 2 weeks between each experiment was used, that is between investigation of the effect of xenon administration on the EEG and R-MUA, effect of nitrous oxide administration on the EEG and R-MUA, and SEP recording during administration of both agents. The order of the experiments was always the EEG experiments first, followed by the SEP studies. In some cases the interval was more than 3 months. We were unable to maintain good recording conditions for the SEP experiment in three cats, and therefore we used three new cats for these studies.

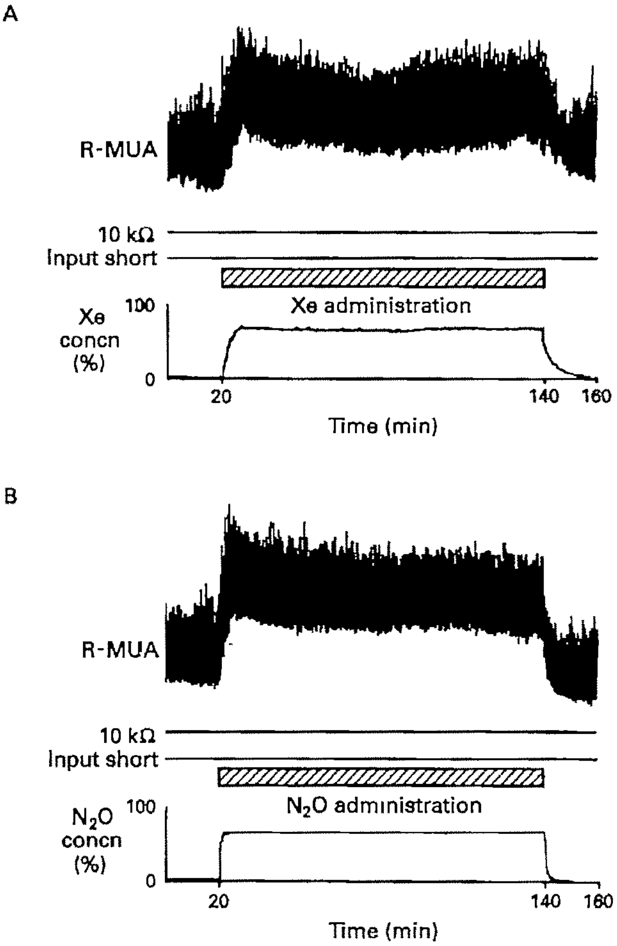

Figure 4 Typical recordings of changes in R-MUA during administration of 70% xenon (Xe) (A) or 70% nitrous oxide (N_2O) (B) in a cat anaesthetized with 5% sevoflurane. The lines labelled "10 kΩ" and "input short" are the levels of R-MUA obtained when inserting a 10-kΩ resistor or a short across the input in place of the animal. The lower trace is the concentration of xenon or nitrous oxide sampled from the proximal end of the tracheal tube

For EEG and R-MUA recordings, the animals were first anaesthetized with 5% sevoflurane in oxygen in the anaesthesia box. A hind limb vein was cannulated for infusion of fluids and drugs. Vecuronium 4 mg was given i.v. and the trachea intubated. In the case of xenon administration, in order to reduce the consumption of xenon, it was administered by manual ventilation of the lungs, using a low-flow, semi-closed breathing system. Nitrous oxide was administered using a non-rebreathing animal ventilator (SN-480-5, Shinano, Tokyo). Concentrations of oxygen, nitrous oxide, carbon dioxide and sevoflurane were monitored continuously, with the gas sample obtained at the proximal end of the tracheal tube, using an anaesthetic gas monitor (Type 1304, Brüel and Kjær, Nærum, Denmark). End-tidal carbon dioxide partial pressure was maintained at approximately 4.0 kPa.[13] In some animals, xenon concentration was monitored continuously using a xenon gas monitor (Anzai Sogyo, Tokyo). Body temperature was maintained at approximately 38°C using an automatically regulated heating lamp and pad (ATB-1100, Nihon Kohden, Tokyo).[13]

The inspired sevoflurane concentration was initially set at 2% or 5% for at least 30 min, and then the EEG and R-MUA were recorded. Twenty minutes after the start of recording, the inspired gas was

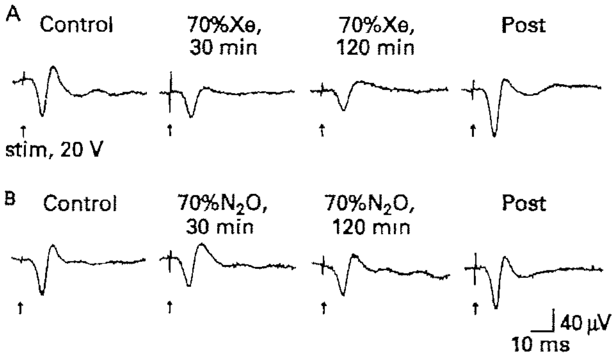

Figure 5 Typical recordings of the effects of administration of xenon (Xe) or nitrous oxide (N_2O) on cortical somatosensory evoked potentials (SEP) in a cat anaesthetized with 2% sevoflurane.

changed from oxygen to 70% xenon in oxygen or 70% nitrous oxide in oxygen, with the inspired sevoflurane concentration unchanged. Either xenon or nitrous oxide was administered for 2 h, and then replaced with the preceding gas mixture of oxygen and sevoflurane. CNS electrical activity was recorded for 20 min to confirm recovery. When both concentrations of sevoflurane were used as basal anaesthesia on the same animal on the same day, at least 1 h was allowed between each recording.

Recording of SEP was performed on different days. Basal anaesthesia with 2% sevoflurane was used. The SEP was recorded 20 min before, every 30 min during and 20 min after xenon or nitrous oxide administration. The anaesthetics were administered for 2 h, at random, to the same animal on the same day. The interval between xenon and nitrous oxide administration was at least 1 h.

DATA ANALYSIS

Values for R-MUA and SEP were analysed using a computer program (Scope or Chart, AD Instruments, Castle Hill, Australia). The R-MUA signal was measured every 5 min as the distance from the lower limit of the rectified trace to the 10-kΩ resistor line. With regard to the SEP, the amplitude and peak latency periods of the initial positive (P1) and negative (N1) deflections were measured. For R-MUA, baseline values were determined for an average time of 20 min before administration of anaesthetic gas, and all data were expressed as mean (SEM) percentage of baseline values. The values obtained immediately before xenon or nitrous oxide administration served as controls. Statistical analysis was performed by analysis of variance (ANOVA) using Statview 4.11J. When appropriate, *post hoc* comparisons (Fisher's protected least significant difference test) were performed. $P<0.05$ was considered significant.

Results

EFFECTS ON THE EEG

The EEG after 2% sevoflurane anaesthesia consisted of high-amplitude slow waves in the cortex and amygdala, and delta waves of 2–2.5 Hz in the dorsal hippocampus, as reported previously (fig. 1A, control).[9] Xenon 70% initially induced rhythmic theta and delta slow waves in the cortex, occasional spike activities in the amygdala and slow waves in the dorsal hippocampus, in all six animals (fig. 1A, 30 min). Of the six cats, four developed bursts of high-amplitude sharp waves of 1–3 Hz interrupted by low-amplitude slow waves, in all three recording sites, 30–60 min later (fig. 1A, 90 min). The pattern of bursts of high-amplitude sharp waves interrupted by low-amplitude slow waves was occasionally replaced by the preceding EEG pattern. In the remaining two animals, the initial EEG pattern persisted during the observation period of 2 h. With 5% sevoflurane, the EEG consisted of high-amplitude spike activities and low-voltage slow waves in all three recording sites, as reported previously (fig. 1B, control).[9] Xenon 70% increased the frequency of high-amplitude spikes (fig. 1B, xenon administration).

Nitrous oxide 70% induced a decrease in amplitude, with frequency unchanged, in the cortex and amygdala, and an increase in the frequency of the dorsal hippocampus EEG, during 2% sevoflurane anaesthesia (fig. 2A, nitrous oxide administration). With 5% sevoflurane anaesthesia, nitrous oxide increased the frequency of high-amplitude spikes (fig. 2B, nitrous oxide administration). In four of six animals, nitrous oxide induced rhythmic sine curve waves of 10 Hz between the high-amplitude spikes (fig. 2B, nitrous oxide administration), as reported previously.[7]

EFFECTS ON R-MUA

The effects of 70% xenon on R-MUA during 2% sevoflurane anaesthesia were variable. Of the six cats, four showed an initial increase which then fluctuated. R-MUA changes correlated with cortical EEG changes: an increase in R-MUA was associated with cortical rhythmic theta and delta slow waves, and a decrease with bursts of high-amplitude sharp waves interrupted by low-amplitude slow waves. In the two other cats, R-MUA showed a sustained increase with the EEG showing cortical rhythmic slow waves. For the average value, R-MUA showed a tendency to increase initially followed by a decrease with xenon (fig. 3A). In contrast, a sustained increase was observed with 5% sevoflurane (figs 3B, 4A). In

Table 1 Effect of xenon (Xe) or nitrous oxide (N_2O) on the somatosensory evoked potential (P1) (mean (SEM)) during 2% sevoflurane anaesthesia in the cat (*n*=6). **P*<0.05 compared with control, as determined by Fisher's protected least significant difference test. The latency of N_2O was not significantly different, as determined by factorial ANOVA

	Xe latency (ms)	Xe amplitude (%)	N_2O latency (ms)	N_2O amplitude (%)
Control	7.8 (0.5)	100	8.9 (0.7)	100
30 min	9.7 (0.5)*	77 (10)*	8.5 (0.8)	71 (8)*
60 min	9.8 (0.6)*	64 (7)*	8.6 (0.7)	71 (8)*
90 min	10.0 (0.3)*	69 (10)*	8.6 (0.8)	76 (9)*
120 min	9.2 (0.5)	71 (8)*	8.7 (0.8)	72 (9)*
Post	8.2 (0.5)	86 (9)	9.2 (0.7)	94 (4)

Table 2 Effect of xenon (Xe) or nitrous oxide (N_2O) on the somatosensory evoked potential (N1) (mean (SEM)) during 2% sevoflurane anaesthesia in the cat (n=6). *P<0.05 compared with control, as determined by Fisher's protected least significant difference test. Both the latency and amplitude of N_2O were not significantly different, as determined by factorial ANOVA

	Xe latency (ms)	Xe amplitude (%)	N_2O latency (ms)	N_2O amplitude (%)
Control	12.9 (0 3)	100	14.0 (0.7)	100
30 min	16.5 (0.9)*	58 (11)*	15.1 (0.8)	76 (10)
60 min	17 (1.3)*	48 (8)*	14.5 (0.7)	84 (18)
90 min	16.3 (0.8)*	38 (11)*	14.6 (0.8)	87 (14)
120 min	16.2 (0.7)*	58 (11)*	15.0 (0.7)	89 (13)
Post	13.4 (0.5)	75 (8)	14.2 (0.6)	88 (17)

contrast, 70% nitrous oxide induced a sustained increase in R-MUA with both 2% and 5% sevoflurane anaesthesia (figs 3, 4B). There were no significant differences between xenon and nitrous oxide on R-MUA with 5% sevoflurane (fig. 3B).

EFFECTS ON SEP

Xenon 70% produced a small decrease in P1 amplitude and a greater decrease in N1 amplitude. Xenon slightly prolonged the peak latent period of both deflections (fig. 5, tables 1, 2). Nitrous oxide 70% slightly depressed P1 amplitude, but N1 amplitude was unaffected. The latent periods of both deflections were not affected by nitrous oxide (fig. 5, tables 1, 2). There was a significant difference between 70% xenon and 70% nitrous oxide for the effects on N1 amplitude (table 2).

Discussion

We have demonstrated that during 5% sevoflurane anaesthesia, xenon and nitrous oxide had similar effects on the EEG and R-MUA, that is activation of CNS activity. However, during 2% sevoflurane anaesthesia, the CNS actions of xenon were variable and both CNS stimulation and depression were confirmed: initial stimulation followed by suppression was observed in four of six animals while sustained activation was observed in the remaining two animals. In contrast, nitrous oxide always stimulated the CNS. Furthermore, xenon suppressed SEP to a greater extent than nitrous oxide.

As we used animals anaesthetized with sevoflurane, the pharmacological action of the anaesthetics studied were therefore confounded by the action of sevoflurane, a convulsive anaesthetic. The use of sevoflurane was essential for ethical reasons as nitrous oxide is a weak anaesthetic and could not be studied alone.

Morris, Knott and Pittinger first described the EEG changes during surgery using xenon anaesthesia in patients. They observed depression of alpha activity and a low-voltage fast wave pattern in the initial stage, followed by rhythmic slow waves.[14] Although the exact concentration of xenon was not documented, considering that the operation was performed with xenon alone, the concentration was probably greater than 70%. Recently, the effects of low concentrations of xenon on the EEG in humans and baboons have been reported.[15–17] Hartmann and colleagues reported that 35% xenon induced theta and delta activities on the EEG.[15 16] In contrast, Sclabassi and colleagues showed that 25–35% xenon induced no EEG slowing.[17] Our study, using cats, confirmed previous studies of xenon-induced theta and delta rhythmic waves in the cortex in humans and baboons.[15 16]

One of the authors (K. M.) has classified general anaesthetics into three types based on CNS electrical activity: depressant, excitant and epileptogenic anaesthetics.[18] The CNS excitant anaesthetics, such as nitrous oxide, ether, ketamine and cyclopropane, induce rhythmic theta and delta slow waves on the EEG associated with an increase in R-MUA. The excitatory action of nitrous oxide in our study confirmed these views and our previous studies.[5 7 19] Furthermore, surgical noxious stimulation and stimulation by i.v. administration of depolarizing neuromuscular blocking agents, which have potent CNS activating actions, also produced rhythmic theta and delta slow waves in human infants and children anaesthetized with halothane.[10 20] Surgical stimulation induced similar rhythmic slow waves in adult humans anaesthetized with halothane.[21] Recently it was reported that mental effort such as calculation induces rhythmic theta waves on the EEG and in magnet-encephalography.[22] Although experimental and clinical settings are very different, collectively these findings indicate that induction by xenon of rhythmic theta and delta slow waves on the EEG which were associated with an increase in R-MUA in this study, represent CNS stimulation, and that xenon should also be classified as a CNS excitant anaesthetic.

The actions of xenon were both stimulating and suppressive on the CNS with 2% sevoflurane anaesthesia. However, it stimulated the CNS when the animals were more deeply anaesthetized with 5% sevoflurane. Such dual effects were not observed with nitrous oxide. Both nitrous oxide and xenon suppressed SEP. However, greater suppression of SEP was confirmed with xenon than with nitrous oxide. The greater suppressive action of xenon on the SEP and suppression observed by xenon on the EEG and R-MUA in lightly anaesthetized animals indicate that xenon has greater CNS suppressive actions than nitrous oxide. Greater suppression of R-MUA with 5% sevoflurane anaesthesia was required to demonstrate constant enhancement by xenon. This may be explained if we postulate that CNS stimulation by xenon is weak, and becomes evident when the activity is deeply suppressed by sevoflurane. The relative resistance of CNS stimulation by nitrous oxide to the depressant action of sevoflurane may be similar to resistance of the CNS stimulating action of nitrous oxide to the suppressive action of enflurane.[7]

The greater suppressive action of xenon compared with nitrous oxide agrees with a MAC study in humans: the MAC of xenon is 71%,[2] while that of nitrous oxide is 105%.[23] Similarly, the oil:gas partition coefficient of xenon (1.9) is greater than that of nitrous oxide (1.4).[24] Xenon 70% required a lower dose of fentanyl than 70% nitrous oxide to maintain an adequate depth of anaesthesia.[4,25] The greater suppressive action of xenon compared with nitrous oxide on CNS reactive capability suggests that xenon is more suitable for anaesthesia than nitrous oxide.

Nitrous oxide exerts its analgesic action not only via a direct action on the intraspinal nociceptive cells but also via an indirect action by activating the descending inhibitory system.[26] The stimulatory actions of xenon on R-MUA in our study suggest that activation of the descending inhibitory system may be involved in the suppressive action of xenon on spinal neurones.[11]

In summary, xenon had a stimulatory action on CNS background activity and a suppressive action on CNS reactive capability. These neurophysiological properties of xenon are similar to those of nitrous oxide and suggest that xenon is an excitatory anaesthetic. The more potent suppressive action of xenon compared with nitrous oxide on CNS reactive capability suggests that xenon is a valuable alternative to nitrous oxide.

Acknowledgments

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Effect of isoflurane on release and uptake of γ-aminobutyric acid from rat cortical synaptosomes

M. Larsen, T. S. Haugstad, J. Berg-Johnsen and I. A. Langmoen

Summary

We have studied the effect of isoflurane on potassium-evoked release and high-affinity uptake of γ-aminobutyric acid (GABA) in rat cortical synaptosomes. Isoflurane 1.5% and 3% increased calcium-dependent release by 38% and 36% of control values, respectively ($P<0.05$). Calcium-independent release was reduced correspondingly by 24% and 26% ($P<0.05$). High-affinity uptake of GABA was not affected by isoflurane. The findings of increased synaptic GABA release combined with unaltered uptake suggest that isoflurane increases GABA in the synaptic cleft and thus may enhance inhibition. (*Br. J. Anaesth.* 1998; **80**: 634–638)

Keywords: anaesthetics volatile, isoflurane; nerve, transmission; nerve, neurotransmitters; brain, GABA; nerve, synaptosome; rat

Isoflurane reduces excitatory activity in rat cerebral cortex[1] by depression of the activity of thin unmyelinated fibres,[2] reduction of excitatory synaptic transmission[3 4] and hyperpolarization of the postsynaptic neurone.[5 6]

The effect on synaptic transmission seems to be the most important quantitatively.[3 7] We have shown previously that isoflurane reduced both synaptic (calcium-dependent) and non-synaptic (calcium-independent) release of glutamate in rat cerebral cortex,[8] while the postsynaptic response was unchanged.[4] Furthermore, isoflurane increased the uptake of the transmitter glutamate in the presynaptic terminal in a dose-dependent manner.[9] These changes may produce reduced transmitter levels in the synaptic cleft and thus attenuate excitatory mechanisms.

The effect of anaesthetic agents on inhibitory synaptic transmission has not been studied in detail. γ-Aminobutyric acid (GABA) is the major inhibitory transmitter in the mammalian brain.[10] During membrane depolarization of the presynaptic terminal, GABA is released by exocytosis of the calcium-dependent pool located in a non-cytoplasmic compartment.[11] This is consistent with synaptic GABA release, which is calcium-dependent. In contrast, calcium-independent release appears to result from reversal of the sodium-dependent uptake carrier and thereby efflux of GABA from a non-synaptic, cytoplasmic compartment.[11] The $GABA_A$ receptor–channel complex seems to represent a major target for most of the general anaesthetics in use.[7] According to some electrophysiological studies, volatile anaesthetics potentiate inhibition, as demonstrated by prolongation of both inhibitory postsynaptic potentials (IPSP)[12] and inhibitory postsynaptic currents (IPSC).[13 14] However, other studies have shown that these anaesthetics depress both presynaptic[15] and postsynaptic inhibition.[16 17] As inhibitory interneurones are activated by excitatory afferents,[18–20] the degree of inhibition is thus dependent on excitatory input, amount of GABA available in the synaptic cleft and effects on postsynaptic receptors.

To investigate a potential effect of isoflurane on inhibition in the cerebral cortex, we measured calcium-dependent release and high-affinity uptake of GABA using synaptosomes from rat cerebral cortex.

Materials and methods

PREPARATION OF SYNAPTOSOMES

Synaptosomes were prepared as described by McMahon and colleagues.[21] Briefly, Wistar rats, treated according to approved rules, were killed by decapitation and the brain removed carefully. The cortex from each hemisphere was dissected, placed in 15 ml of sucrose 0.32 mol $litre^{-1}$ (1–4°C) and homogenized in a glass homogenizer with a Teflon pestle (clearance=0.25 mm). The homogenate was then centrifuged for 3 min at 3000×*g* and the supernatant spun for 30 min at 15 000×*g*. The pellet formed was two layered. The superficial layer containing the majority of the synaptosomes[21] was resuspended selectively in 6 ml of sucrose 0.32 mol $litre^{-1}$, stored at 1–4°C and used within 6 h from preparation. When used for release experiments, the pellets were diluted in calcium-free HEPES-buffered medium (HBM), containing (mmol $litre^{-1}$): NaCl 117.5, KCl 3.75, $MgCl_2$ 1, KH_2PO_4 1.25, $NaHCO_3$ 20, glucose 10, HEPES 20 and NaOH 6 (pH 7.4). For uptake experiments, HBM also contained $CaCl_2$ 1.3 mmol $litre^{-1}$. HBM was made daily.

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Table 1 Release of GABA from rat cortical synaptosomes. Effect of potassium depolarization and 0.5%, 1.5% and 3.0% isoflurane. Depol.=Depolarization; Depol./0 Ca^{2+}=depolarization with calcium-free medium (blocked synaptic transmission). Values are mean (SEM), n=7. *P<0 05 compared with control

	GABA release (pmol mg^{-1} min^{-1})		
Group	Basal release	Depol.	Depol./0 Ca^{2+}
Control	59 (23)	181 (18)*	128 (11)*
Isoflurane 0.5%	46 (12)	168 (12)*	128 (13)*
Isoflurane 1.5%	49 (28)	183 (32)*	110 (20)*
Isoflurane 3.0%	82 (9)	185 (21)*	113 (13)*

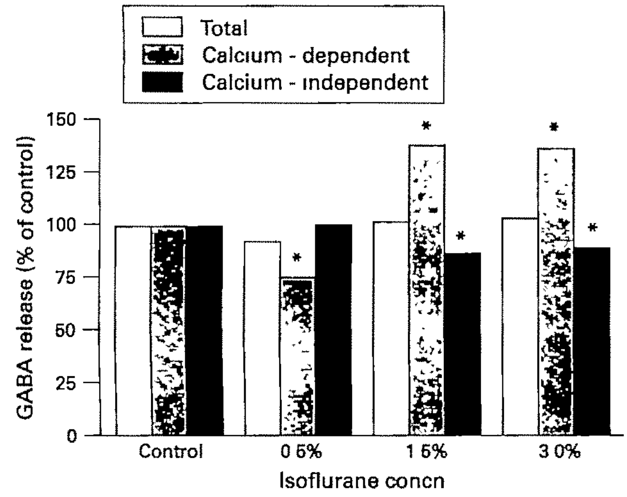

Figure 1 Effect of 0 5%, 1.5% and 3.0% isoflurane on potassium-evoked GABA release in rat cortical synaptosomes. GABA release (total, calcium-dependent and calcium-independent) was estimated as a percentage of control values (n=7). *P<0.05. For variability data, see table 1.

GABA RELEASE

Synaptosomes (2–4 mg protein ml^{-1} in each chamber) were diluted in six different sealed chambers containing calcium-free HBM and saturated with 95% oxygen–5% carbon dioxide. CaCl$_2$ 1.3 mmol litre^{-1} was added to wells 1–4 and EGTA 150 mmol litre^{-1} (Sigma Chemicals, St Louis, MO, USA) to wells 5 and 6 (in order to block synaptic transmission); wells 2, 4 and 6 were supplied with isoflurane (Abbott Laboratories Ltd, Kent, UK) using a vaporizer (Fortec, Ohmeda 5250 RGM, Englewood, CA, USA) at a flow rate of 300 ml min^{-1}. After 15 min, KCl 30 mmol litre^{-1} was added to wells 3–6. Each chamber with a volume of 1.0 ml contained 300 μl of the incubation medium. Release was terminated after 2 min by centrifugation, as 2 min is sufficient to mobilize calcium-dependent release, whereas later release is mainly non-synaptic,[22 23] and one should still be (although late) in the initial linear phase of release. Temperature was maintained at 37 (±1)°C throughout the experiment.

Tissue was collected at the end of the experiment to measure the protein content in each well.[24] Samples from the test wells were cleaned and deproteinized by ultracentrifugation through a 5x10^{3} Dalton cut-off filter (Nihon Millipore, Yonezava, Japan). The content of amino acids was detected by high pressure liquid chromatography (HPLC) (Perkin Elmer, Norwalk, CT, USA) after pre-column derivatization with *o*-phthalaldehyde, as described previously.[25] Until analysed, samples were stored at −70°C.

Table 2 Uptake velocity (μmol g^{-1} min^{-1}) of GABA at different concentrations covering the high affinity range in the synaptosome fraction from rat cerebral cortex The effects of 0.5%, 1.5% and 3 0% isoflurane were tested. Values are mean (SEM), n=7

	GABA concentration (x10^{-5} mol litre^{-1})			
Group	0.55	0 70	1.60	2.50
Control	0.07 (0.010)	0.08 (0.007)	0.10 (0 010)	0.12 (0.010)
Isoflurane 0.5%	0.08 (0.010)	0.08 (0.010)	0.10 (0.020)	0.11 (0.020)
Isoflurane 1.5%	0.07 (0.007)	0 08 (0.012)	0.09 (0.007)	0.10 (0.011)
Isoflurane 3.0%	0.08 (0 006)	0.08 (0.006)	0.10 (0.005)	0.12 (0.007)

GABA UPTAKE

Synaptosomes (2–4 mg protein ml^{-1}) were incubated at 37°C in chambers containing different concentrations of GABA corresponding to the high-affinity uptake system (5.5x10^{-6}–2.5x10^{-5} mol litre^{-1}).[26] A fixed concentration (1.8x10^{-9} mol litre^{-1}) of radiolabelled GABA (46 Ci mmol^{-1}) (Amersham Laboratories, Buckinghamshire, UK) was added to each batch. The chambers, each containing 1.5 ml of incubation medium, were sealed and saturated with 95% oxygen–5% carbon dioxide. Isoflurane (0.5%, 1.5% or 3.0%) was added using a vaporizer at a flow rate of 300 ml min^{-1} and the medium shaken gently every 30 s. Uptake was terminated at 4 min as the synaptosomes were placed on a Millipore filter (polyvinylidene difluoride filter, pore size 0.65 μm), washed in 5 ml of 0.9% NaCl (1–4°C) and dissolved in 1 ml of 10% Triton X-100 for 10 min. The suspension was removed from the filter and scintillation fluid (Pico-Fluor 15, Packard, Groningen, the Netherlands) added. Labelling was measured by counting disintegrations per minute in a β-scintillation counter (LKB Wallac, San Fransisco, CA, USA) with a counting efficiency of 25–30%. Protein content was measured according to the method of Lowry and colleagues.[24]

In both release and uptake experiments, a control experiment and experiments using 0.5%, 1.5% and 3.0% isoflurane were performed using one batch of synaptosomes prepared from one brain. The number of experiments (n=7) reflects the number of rats used.

Results are presented as mean (SEM). Differences between two individual groups were tested using the Wilcoxon signed rank sum test and for three or more groups using the Kruskal–Wallis test. Differences were considered significant when P<0.05. The statistical package used was StatView 4.1.

Results

Membrane depolarization with potassium 30 mmol litre^{-1} evoked an increase in GABA release from 59 (23) to 181 (18) pmol mg^{-1} min^{-1} (P<0.05) (table 1). Addition of isoflurane produced no significant change in total GABA release (table 1, fig. 1). Release during blocked synaptic transmission (calcium-free medium) was unaltered when 0.5% isoflurane was added, but was reduced by 1.5% and 3.0% isoflurane to 86% and 88% of control values, respectively

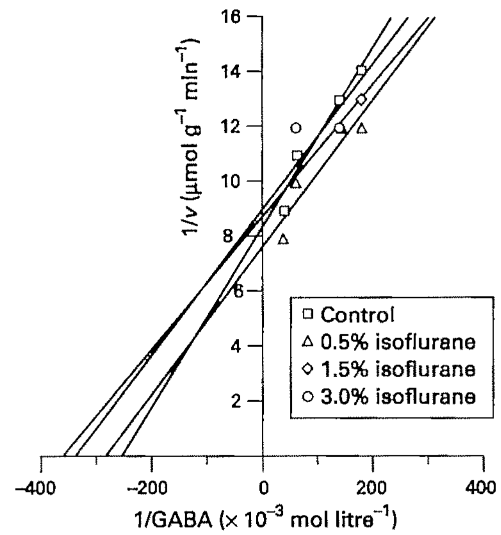

Figure 2 Double-reciprocal plot of the effect of 0.5%, 1.5% and 3.0% isoflurane on high-affinity uptake of GABA in synaptosomes. Regression lines are drawn for controls (r^2=0.943), 0.5% isoflurane (r^2=0.877), 1.5% isoflurane (r^2=0.727) and 3.0% isoflurane (r^2=0.821). Each symbol represents the mean of seven experiments.

Table 3 Effect of 0.5%, 1.5% and 3.0% isoflurane on estimated K_m and *v*max values for uptake of GABA into synaptosomes. Values are mean (SEM), *n*=7

Test group	K_m ($\times10^{-4}$ mol litre^{-1})	*v*max (μmol g^{-1} min^{-1})
Control	3.86 (0.48)	0.12 (0.02)
Isoflurane 0.5%	2.76 (0.34)	0.12 (0.02)
Isoflurane 1.5%	2.91 (0.58)	0.11 (0.02)
Isoflurane 3.0%	3.53 (0.64)	0.13 (0.02)

($P<0.05$) (table 1, fig. 1). Synaptic (calcium-dependent) GABA release was calculated by subtracting non-synaptic (calcium-independent) release from total GABA release. Isoflurane 0.5% produced a decrease in release to 75%, while 1.5% and 3.0% isoflurane increased release to 138% and 136%, respectively, compared with release without isoflurane ($P<0.05$) (fig. 1).

Uptake of GABA into the presynaptic terminal was measured in the concentration range 5.5×10^{6}–2.5×10^{-5} mol litre^{-1}, corresponding to the high-affinity transporter. Uptake velocity was measured under control and 0.5%, 1.5% and 3.0% isoflurane conditions. Isoflurane had no effect on uptake velocity compared with controls at any concentration. The results are summarized in table 2. By plotting the mean values according to Lineweaver–Burk (double reciprocal plot), straight lines with regression coefficients of 0.727–0.943 were produced (fig. 2). In the control samples, K_m was 3.86 (0.48) μmol litre^{-1} and *v*max 0.12 (0.02) μmol g^{-1} min^{-1}. There was no significant change in K_m or *v*max for any isoflurane concentration. Calculated K_m and *v*max values are presented in table 3.

Discussion

We have demonstrated that 1.5% and 3.0% isoflurane increased synaptic GABA release from presynaptic terminals during membrane depolarization. Isoflurane did not affect the uptake kinetics of GABA. These observations indicate that the amount of GABA in the synaptic cleft may increase during synaptic transmission and thus enhance inhibition. Furthermore, they strengthen the assumption that inhaled anaesthetics exert their effects on both excitatory and inhibitory pathways. Reduced synaptic excitation, however, seems to be quantitatively the most important effect.[3] Isoflurane reduced the amount of glutamate in the synaptic cleft during synaptic transmission as calcium-dependent release was decreased[8] and re-uptake was enhanced.[9] The effects on inhibitory pathways have not yet been studied in detail, as inhibitory potentials are small and easily contaminated by excitatory currents.

Presynaptic terminals (synaptosomes) are well used for studies of release and uptake mechanisms.[27] Both calcium-dependent release[11] and high-affinity uptake[28] of GABA have been demonstrated. Thus isolated nerve terminals were chosen for investigation of a potential effect of isoflurane on inhibitory signal transduction.

Isoflurane at the lowest concentration reduced synaptic GABA release, whereas at higher concentrations release was increased. Non-synaptic GABA release was reduced by 1.5% and 3.0% isoflurane. Total GABA release was unchanged. This anaesthetic effect on endogenous calcium-dependent GABA release has, to our knowledge, not been reported previously. The early increase in synaptic GABA release and resultant increase in inhibition is in keeping with electrophysiological findings in hippocampal pyramidal neurones showing an initial increase in amplitude of inhibitory postsynaptic potentials (IPSP),[17] followed by dose-dependent reduction when 3% and 5% isoflurane were added. Similar biphasic actions of anaesthetics have been reported by others.[17 29-32] As depolarization-induced, calcium-independent GABA release was measured, however, it cannot be ruled out that at least some of the GABA could be released into the synaptic cleft during synaptic transmission. As calcium-independent release is reduced with increasing isoflurane concentration, this could to some extent modify the effect of the anaesthetic-induced increase in calcium-dependent GABA release.

Decreased inhibition as a result of reduced synaptic GABA release during administration of 0.5% isoflurane could explain in part the transient hyperexcitation phase observed during induction of anaesthesia. As 1.5% and 3.0% isoflurane increase the amount of GABA in the synaptic cleft during synaptic transmission, the GABA receptor–channel complex is activated, and increased chloride influx would tend to hyperpolarize the cells by moving the membrane potential away from the firing threshold and thus reducing excitability. Most i.v. anaesthetic agents enhance $GABA_A$ receptor-mediated synaptic inhibition.[7] Pentobarbital and ketamine increase the time constant of decay of inhibitory postsynaptic currents (IPSC) in the rat hippocampus, probably by stabilizing the open state of GABA-activated channels.[14] Similarly, halothane, enflurane and isoflurane increase $GABA_A$-activated chloride currents in cultured hippocampal neurones[33] by prolonging the opening time of the receptor–channel complex rather than altering conductance.[7] As anaesthetics seem to increase the currents evoked by low concentrations of GABA, but have no effect at high GABA concentrations,[34-36] enhanced affinity for GABA is the most plausible explanation for the anaesthetic-induced potentiation of the GABA response.

If general anaesthetics exert their effects mainly by disrupting signal transduction in afferent nerves, the effect on excitatory and inhibitory synaptic transmission would be the same;[37] either enhancement or depression of both. However, barbiturates inhibit depolarization-evoked release of glutamate and aspartate from brain slices,[38-41] while both pre- and postsynaptic inhibition are enhanced.[12 14 15 35 42 43] In hippocampal neurones, pentobarbital and halothane induce activation of chloride currents mediated by the $GABA_A$ receptor–channel complex via different mechanisms. Pentobarbital seems to act directly at the receptor–channel complex, while the effects of halothane are dependent on an increase in intracellular calcium, supporting a multi-site hypothesis for anaesthesia.[44] Halothane, and to some extent isoflurane, increase phosphorylation of several brain cytoplasmic proteins via stimulation of protein kinase C (PKC) in a calcium- and phospholipid-dependent manner.[45] The $GABA_A$ receptor–channel complex has a particular γ-subunit containing an amino acid sequence with a phosphorylation site for PKC.[46] The potentiating effect of isoflurane on the $GABA_A$ receptor–channel complex could be explained by anaesthetic-induced activation of PKC.

During cerebral ischaemia, both excitatory amino acids[47 48] and GABA[49 50] are released in a calcium-independent or non-synaptic manner. Extracellular concentrations of sodium, chloride and calcium decrease during ischaemia,[51] possibly as a result of increased influx of these ions followed by water, causing intracellular oedema and neuronal damage. The isoflurane-induced effect on calcium-independent GABA release could thus be of interest, as reduction in GABA release and attenuated chloride influx during ischaemia improves neuronal recovery.[52]

We have described isoflurane-induced increase in synaptic GABA release accompanied by unchanged uptake of transmitter. The amount of GABA in the synaptic cleft should thus be enhanced, in keeping with previous studies,[12-14] suggesting anaesthetic-induced enhancement of synaptic inhibition.

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Effects of diaspirin cross-linked haemoglobin on post-traumatic cerebral perfusion pressure and blood flow in a rodent model of diffuse brain injury

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Summary

Diaspirin cross-linked haemoglobin (DCLHb) is a new oxygen carrying blood substitute with vasoactive properties. Vasoactive properties may be mediated via high affinity binding of nitric oxide by the haem moiety. Using a rodent model of head injury combined with ischaemia, we studied the effects of DCLHb on cerebral blood flow (CBF) and intracranial pressure (ICP). Twenty anaesthetized rats were allocated randomly to receive treatment with DCLHb 400 mg kg^{-1} i.v. or placebo (oncotically matched plasma protein substitute 4.5% i.v.). To produce diffusely increased ICP, after a severe weight drop injury, all animals underwent a 30-min period of bilateral carotid ligation combined with a period of induced hypotension. After reperfusion, DCLHb or placebo was infused and the animals instrumented for measurement of intraventricular ICP and CBF in the region of the sensorimotor cortex using the hydrogen clearance technique. Mean arterial pressure (MAP), ICP, cerebral perfusion pressure (CPP) (CPP=MAP–ICP) and CBF were measured 4 h after injury in all animals. DCLHb significantly reduced ICP from mean 13 (SEM 2) to 3 (1) mm Hg (P<0.001), increased CPP from 52 (8) to 95 (6) mm Hg (P<0.001) and increased CBF from 21 (2) to 29 (2) ml 100 g^{-1} min^{-1} (P=0.032). We conclude that DCLHb improved CPP without a reduction in CBF in a rodent model of post-traumatic brain swelling. (*Br. J. Anaesth.* 1998; **80**: 639–643)

Keywords: blood, replacement; brain, blood flow; brain, injury; brain, intracranial pressure; rat; model, rat

Head injury is one of the commonest causes of death and disability associated with trauma.[1,2] The non-surgical management of the severely head injured patient involves prevention of secondary insults such as arterial hypotension and hypoxaemia. Increased intracranial pressure (ICP) also occurs frequently after head injury and is a common secondary insult which significantly contributes to patient morbidity and mortality.[3,4] More than 70% of severely head injured patients exhibit one or more episodes of increased ICP (ICP >20 mm Hg).[4,5] Although there are several useful adjuncts for the management of increased ICP, including the use of osmotic and other diuretics to attempt to control tissue oedema, and agents which modify the rheology of blood in order to better perfuse the brain, the range of effective agents for treating increased ICP is limited.

Diaspirin cross-linked haemoglobin (DCLHb) is a new solution manufactured from human haemoglobin, harvested from outdated donated blood. The haemoglobin molecules are cross-linked at the α chains by treatment with the salicylate bis(3,5-dibromosalicyl) fumarate.[6] This process forms a solution which is chemically stable, has low viscosity, a longer intravascular retention time than haemoglobin monomers or dimers, and an oxygen carrying capacity similar to whole blood.[7]

During preclinical studies DCLHb increased arterial pressure and preferentially redistributed blood flow to the brain and other vital organs.[8] This increase in arterial pressure was caused in part by generalized vasoconstriction which may include a cerebral vasoconstrictor component. Therefore, DCLHb seems to have potential as a neuroprotective agent by its ability to vasoconstrict, increase arterial pressure and yet maintain or augment oxygen delivery to tissues by virtue of its low viscosity and oxygen carrying capacity. To test the hypothesis that DCLHb may have beneficial effects on cerebral blood flow (CBF) and ICP without worsening brain perfusion, we compared its effects with standard treatment in an established rodent model of head injury-induced diffuse brain swelling.[9,10]

Materials and methods

The study conformed to the UK Home Office Animals Scientific Procedures Act 1986 (PPL 60/01228). We studied 20 male Sprague–Dawley rats (350–450 g), allocated randomly to a placebo (n=10) or treatment group (n=10). For induction of anaesthesia, all animals were placed in a holding cage containing 4% halothane in oxygen. When anaesthesia was induced, the animals were given diazepam 2.5 mg kg^{-1} i.p., in Hypnorm (fentanyl-based 0.3 ml kg^{-1}) to provide surgical anaesthesia for the time required to obtain i.v. access. Anaesthesia was maintained

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Table 1 Physiological variables monitored during application of secondary insults after the injury (mean (SEM))

	MAP (mm Hg)	Pa_{O_2} (kPa)	Lactate (mmol litre^{-1})	Glucose (mmol litre^{-1})
Placebo group	46.1	26.3	5.0	4.7
(n=9)	(2.5)	(4.7)	(1.6)	(0.93)
DCLHb group	48.1	29.1	5.5	7.8
(n=9)	(0.66)	(5.1)	(1.1)	(1.3)

throughout the experiment by continuous infusion of propofol 2.5 µg kg^{-1} min^{-1}. All animals received the same total dose of propofol. Intubation, paralysis with pancuronium 4 mg kg^{-1} h^{-1} and mechanical ventilation with an oxygen–air mix followed for the duration of the study. Bilateral arterial and venous femoral cannulae were inserted for administration of fluids and blood sampling for measurement of arterial blood-gas tensions, packed cell volume (PCV) and serum glucose and lactate concentrations. In preparation for receiving a closed head injury using the Richmond impact acceleration model, all animals had the musculature overlying the cranium surgically reflected to expose the bregma. All bleeding was stopped and the skull surface dried. In accordance with the standard method, a 1-cm diameter circular metal disk helmet was fixed, using cold curing dental acrylic, to the skull immediately overlying the bregma.

At the start of the study all animals received a severe (450 g×2 m) weight drop head injury using the Richmond impact acceleration model.[9] Following a 30-min stabilization period after the injury, all animals received 30 min of "secondary insults" consisting of bilateral carotid artery ligation coupled with a lowering of mean arterial pressure (MAP) to 40–50 mm Hg. This has been shown previously to produce diffusely increased ICP in this model.[10] Arterial pressure was lowered by phlebotomy. Blood withdrawn was heparinized and kept warm at 37°C in a water bath. After the 30 min of secondary insults, the carotid clips were removed and blood reinfused. Continuous minute by minute computer-based physiological monitoring recorded the "burden" of secondary insults each animal received during the carotid ligation and hypotensive period. Animals were then allocated randomly to the placebo or treatment group. The treatment group received DCLHb 400 mg kg^{-1} given as a slow i.v. infusion over 15 min. Total infusion volume was less than 2 ml. This dose was chosen as it was within the range used in clinical safety and efficacy studies. The placebo group received an identical volume of oncotically matched human plasma protein solution (HPPS).

After treatment, animals were instrumented for measurement of ICP (24-gauge Sprotte needle placed into a lateral ventricle) and CBF using the hydrogen clearance technique.[11] Bur holes were placed bilaterally, 7 mm posterior and 4 mm lateral to the bregma for placement of hydrogen clearance electrodes in the region of the sensorimotor cortex. Electrodes were positioned with the aid of an operating microscope and inserted using a microdrive, directly through the unopened dura to a depth of 1 mm into the cerebral cortex. Electrodes were sealed in place with cold curing dental acrylic. A reference electrode was wrapped in saline-soaked gauze and placed in a subcutaneous pouch. The hydrogen electrodes were polarized (+400 mV relative to the reference electrode) and allowed to stabilize for 1 h after insertion. During CBF measurement, hydrogen gas was administered at a concentration of 10% for 10 min. The hydrogen electrode current during the desaturation phase was sampled online at 1 Hz for the entire desaturation period by a microcomputer-based CBF measurement system.[12] After re-establishment of a stable baseline, a baseline correction algorithm was used to correct for drift in the hydrogen electrode during desaturation compared with pre-hydrogen baseline. The natural log plot was then calculated from the logarithm of the difference between each sampled point and its corresponding baseline value. The first 20 s of desaturation were discarded as potentially contaminated with arterial recirculation artefact. The initial slope index (ISI) was calculated from the slope of the subsequent 1-min period. As this head injury model is one of diffuse brain injury, to obtain a measure of a single cortical CBF value per study, ISI values reported were the average of the two electrodes recorded from both cerebral hemispheres.

A CBF measurement was obtained 4 h after the injury. This took into account a 30-min recovery period, 30 min of secondary insults, 15 min for infusion of DCLHb or HPPS (and a 10-min infusion set-up time), 60 min for surgical preparation of the animal for placement of the CBF electrodes and an intraventricular needle for measuring ICP, and 60 min for the H2 electrodes to stabilize. During this period of preparation, continuous minute by minute computerized monitoring of arterial pressure and core temperature was performed to ensure a stable basic physiology with no further secondary insults. Monitoring alarms were set to detect if MAP decreased to less than 70 mm Hg or core temperature increased to greater than 38.5°C. Arterial blood-gas tensions were obtained every 30 min. The CBF measurement 4 h after injury was recorded and this timing also coincided with previous work

Table 2 Physiological data 4 h after injury (mean (SEM)). $^*P$<0.05, $^*P$<0.05

	ICP (mm Hg)	MAP (mm Hg)	CPP (mm Hg)	CBF (ml 100 g^{-1} min^{-1})	CVR (mm Hg ml^{-1} 100 g^{-1} min^{-1})	ICP pulse (mm Hg)	Pa_{CO_2} (kPa)	Pa_{O_2} (kPa)	pH	Temp (°C)	Sa_{O_2} (%)	HCO$_3$ (mmol litre^{-1})	Lactate (mmol litre^{-1})	Glucose (mmol litre^{-1})	PCV (%)
Placebo	13.4	65.5	52	21.2	2.6	1.7	5.6	20.9	7.22	37.7	97.7	17.6	3.6	3.6	33
(n=9)	(1 6)	(7.0)	(7.8)	(1.9)	(0.44)	(0.1)	(0.3)	(3.1)	(0.03)	(0.1)	(0.5)	(1.4)	(0.9)	(0.9)	(2)
DCLHb	3.4**	98.5**	95.1**	29.7*	3.3	0.64**	5.7	20.8	7.21	37.3	96.3	18.2	5.6	5.2	38
(n=9)	(0.8)	(5.8)	(6.0)	(2.3)	(0.3)	(0.1)	(0.3)	(3.9)	(0.04)	(0.2)	(1.3)	(2.2)	(1.7)	(1.4)	(7)

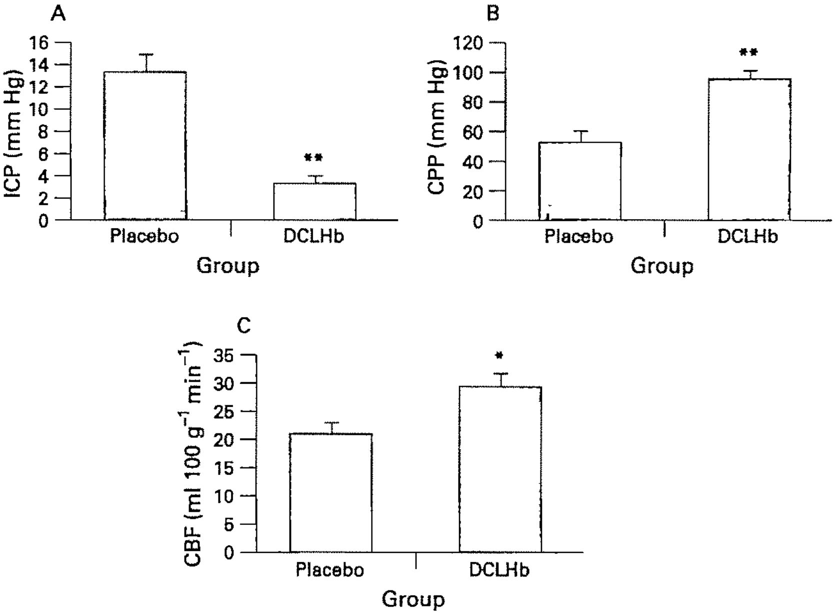

Figure 1 Combination plot comparing the placebo and DCLHb groups in terms of intracranial pressure (ICP) (A), cerebral perfusion pressure (CPP) (B) and cerebral blood flow (CBF) (C) 4 h after injury The hydrogen clearance technique was used for measurement of CBF with the flow from each animal expressed as the mean of left and right cortical values. Values are mean (SEM). $^{*}P<0.05$, $^{**}P<0.01$ (ANOVA).

using this injury paradigm showing the presence of increased CBF by 4 h after injury relative to non-injured controls.[13] Blood-gas tensions, and serum concentrations of glucose and lactate were sampled during the initial slope phase of the CBF measurement, 4 h after injury. The study ended when the CBF measurement 4 h after injury was complete. Blood PCV was measured at the start and end of the study. The animal was killed at the end of the study.

Analysis of variance was used to test for significant differences between the DCLHb and placebo groups. All values are reported as mean (SEM).

Results

Data from two animals were excluded; one animal in the DCLHb group accidentally received a large i.v. bolus of a pressor agent which caused severe arterial hypertension and subsequent metabolic acidosis. This animal died before the end of the study. One animal in the placebo group became extremely hypercapnic (Pa_{CO_2} >9.3 kPa) which could not be controlled by adjustments in mechanical ventilation. As carbon dioxide reactivity is impaired after injury with this model,[13] it would not be valid to normalize CBF data to a normal range of Pa_{CO_2} values. On completion of the study there were nine animals in each group.

Table 1 summarizes MAP, partial pressure of oxygen in blood (Pa_{O_2}) and serum concentrations of lactate and glucose in the two groups, averaged over the 30 min of secondary insults (carotid occlusion with hypotension). There were no significant differences between the placebo and treatment groups in terms of the burden of secondary insults received.

Table 2 summarizes the physiological data (core temperature, Pa_{O_2}, Pa_{CO_2}, pH, arterial oxygen saturation, serum concentrations of bicarbonate (HCO_3), lactate and glucose, and PCV recorded at the time of the CBF measurement, 4 h after the injury. There were no significant differences between the placebo and treatment groups at 4 h for these variables. Table 2 also shows MAP, ICP, ICP pulse, CPP and CBF values recorded at 4 h. The DCLHb group had a significantly higher (P=0.002) MAP (98 (6) mm Hg) compared with the placebo group (65 (7) mm Hg). In addition, a plot of mean ICP showed that the DCLHb group had a significantly lower ($P<0.001$) mean ICP (3.4 (0.8) mm Hg) compared with the placebo group (13.4 (1.6) mm Hg) (fig. 1).

Mean ICP pulse amplitude 4 h after injury, also obtained at the time of CBF measurement, showed that the DCLHb group had a significantly lower (P=0.001) mean ICP pulse amplitude (0.64 (0.1) mm Hg) compared with the placebo group (1.7 (0.15) mm Hg).

As would be expected from the combined results of ICP and MAP, mean CPP (CPP=MAP–ICP) was significantly higher ($P<0.001$) in the DCLHb group (95 (6) mm Hg) compared with the placebo group (52 (8) mm Hg) (fig. 1).

CBF, calculated as the mean of left and right cortical electrode flow values, was significantly higher (P=0.032) in the DCLHb group (29 (2.3) ml 100 g^{-1} min^{-1}) compared with controls (21 (1.9) ml 100 g^{-1} min^{-1}) (fig. 1). There was no significant change in cerebral vascular resistance (CVR=CPP/CBF) with treatment. CVR was 3.3 (0.3) mm Hg ml^{-1} 100 g^{-1} min^{-1} in the DCLHb group compared with 2.6 (0.4) mm Hg ml^{-1} 100 g^{-1} min^{-1} in the placebo group.

Discussion

Increased ICP is a frequent complication of post-traumatic brain injury and can often be difficult to control. It represents a frequently encountered secondary insult which contributes to patient morbidity and mortality. More than 70% of severely head injured patients experience one or more episodes of increased ICP (ICP >20 mm Hg) of which 50–60% exhibit signs of diffuse brain swelling on CT scan.[5] Of these it has been estimated that more than 70% of increased ICP found in diffusely brain injured patients is attributable to vascular mechanisms.[14]

Intracranial hypertension, in the absence of surgically remediable causes, may be treated by several different approaches to reduce ICP while attempting to prevent cerebral hypoperfusion. These include mild hypocapnia, which helps to reduce the contribution of cerebral blood volume to the cause of increased ICP by means of vasoconstriction. Artificial increases in arterial pressure by pressor agents such as norepinephrine or methoxamine encourage perfusion, and osmotic and diuretic treatments may be used to achieve a reduction in the oedematous process associated with disruption of cerebral tissue.

All of the above therapeutic manoeuvres have inherent problems. Osmotic and diuretic methods of reducing brain oedema can lead to high serum osmolarity which may make renal toxicity a risk. Any agent or manoeuvre which causes cerebral vasoconstriction, such as hypocapnia, reduces cerebrovascular blood volume and leads to at least a temporary reduction in ICP. This approach, however, is not without risk. Reducing ICP by cerebral vasoconstriction in individuals who already have compromised brain perfusion can reduce CBF to a degree that brain ischaemia may occur with resultant neurological damage. An approach that induces mild cerebral vasoconstriction yet maintains adequate oxygen delivery to the tissue would be an important advance in this field.

Our work with this model has shown that DCLHb has a significant beneficial effect on reduction of ICP and enhancement of CPP. The way in which DCLHb produces these effects may be via a variety of mechanisms. The vascular tone of the cerebral tree may be altered beneficially to cause a reduction in ICP and thus enhance CPP. This reduction in ICP may have been achieved by cerebral vasoconstriction. The effect of DCLHb on pulse amplitude supports this, as an increase in vasoconstriction leads to a reduction in ICP pulse amplitude by increasing precapillary arteriolar tone.[15 16] However, a significant increase in cerebrovascular resistance was not found, although a trend towards an increase was noted. Despite this, cortical CBF was not only maintained but increased. An increase in CPP and CBF with no significant increase in vascular resistance argues in favour of impaired autoregulation and a pressure passive state. However, with increased arterial pressure, such a scenario invariably results in increased ICP (not in a reduction, as was the case in these studies). This suggests active autoregulatory vasoconstriction. If autoregulation were preserved in these animals, the decrease in ICP may be a reflection of a compensatory cerebral vasoconstriction caused by increased upstream MAP produced by DCLHb. However, work carried out by ourselves and others, using this weight drop model of head injury, has shown that CBF values observed by 4 h were indicative of hyperaemia and that impairment of pressure autoregulation exists.[15 17] Taken together, this work supports the concept that there is vasconstriction caused by a direct action of DCLHb on the cerebrovasculature rather than via a compensatory autoregulatory response to increased MAP. It could also be argued that propofol anaesthesia may effect the autoregulatory response, however, there is evidence that in rodents, although absolute CBF is reduced, pressure autoregulation remains intact.[18]

Regardless of the mechanism and whether or not a pressure passive state exists, our data showed that after administration of DCLHb, perfusion was improved in the face of reduced ICP. We speculate, however, that DCLHb was beneficial in other ways. It may carry significantly more oxygen to damaged tissues than previous therapies and, in addition, by virtue of its low viscosity[7] may penetrate areas of brain that would have previously been ischaemic. Work done in a rabbit model of spinal cord ischaemia[15] showed that there was a reduction in the incidence of permanent paralysis when animals were treated with DCLHb. Studies in rats also showed a significant reduction in the size of an infarct after haemodilution with DCLHb.[20]

The mechanisms responsible for local control of autoregulatory vasomotor tone involve several constitutive endothelial and perivascular agents, including nitric oxide and the endothelins.[21–23] Haemoglobin is known to bind avidly to nitric oxide and this scavenging effect may explain the increase in vascular tone. This hypothesis has been explored in the rat[24] but as yet has to be substantiated in humans. Thus it is feasible that infusion of DCLHb may lead to an increase in the amount of haemoglobin free of any encapsulating membrane, which is likely to increase binding of circulating NO.

In summary, we have demonstrated a beneficial effect of DCLHb on ICP and perfusion pressure in a rodent model of severe head injury. Further work needs to be done to identify the optimal dose level for this agent and to determine if enhanced cerebral perfusion translates into increased oxygen delivery to the tissues and to improved clinical outcome.

Acknowledgements

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In vivo effects of propofol on acetylcholine release from the frontal cortex, hippocampus and striatum studied by intracerebral microdialysis in freely moving rats

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Summary

Using *in vivo* microdialysis, we have investigated the effects of propofol on acetylcholine (ACh) release from various regions of the rat brain. Propofol 25 and 50 mg kg^{-1} i.p. decreased basal ACh release from the frontal cortex by 70% and 85%, respectively. Propofol 25 and 50 mg kg^{-1} i.p. decreased basal ACh release from the hippocampus by 47% and 72%, respectively. However, in rat striatum, propofol 25 mg kg^{-1} i.p. did not affect basal ACh release and 50 mg kg^{-1} i.p. produced slight inhibition of basal ACh release (by 19%) only in the second sample after i.p. injection. In addition, we also examined the pharmacological mechanisms mediating the interaction between propofol and a γ-aminobutyric acid A ($GABA_A$) receptor complex. In the rat hippocampus, local application of bicuculline 1 μmol $litre^{-1}$, a $GABA_A$ receptor antagonist, significantly antagonized the inhibitory effects of propofol 50 mg kg^{-1} i.p. on basal ACh release. In the rat frontal cortex, local application of bicuculline 1 μmol $litre^{-1}$ did not antagonize the inhibitory effects of propofol 50 mg kg^{-1} i.p. on basal ACh release, while systemic application of bicuculline 1 mg kg^{-1} i.p. significantly antagonized the inhibitory effects of propofol 50 mg kg^{-1} i.p. These results suggest that propofol has powerful depressant effects on ACh release from the rat frontal cortex and hippocampus but not from the striatum, indicating that propofol has a "region-selective" anaesthetic action. Further, these results suggest that the inhibitory effects of propofol in the rat hippocampus may involve "intra" hippocampal $GABA_A$ receptors while the inhibitory effects in the rat frontal cortex may be mediated by $GABA_A$ receptors other than "intra" frontal cortex $GABA_A$ receptors. (*Br. J. Anaesth.* 1998; **80**: 644–648)

Keywords: anaesthetics i.v. propofol; parasympathetic nervous system acetylcholine; measurement techniques microdialysis; brain cerebral cortex; brain hippocampus; rat

The effects of anaesthetic agents are complex[1]: they produce loss of consciousness, loss of memory, changes in spontaneous activity, attenuation of protective reflexes, loss of postural reflexes and unfavourable side effects such as hallucinations, euphoria and amnesia. In addition, anaesthetic agents may influence the level or homeostasis of neurotransmitters in the brain, such as dopamine, norepinephrine and acetylcholine (ACh).[1 2] ACh was the first neurotransmitter to be described and cholinergic neurones are distributed widely in the brain.[3 4] Using *in vivo* microdialysis, several studies reported that anaesthetic agents affect ACh release in various brain regions.[3 5–8] Cholinergic mechanisms are known to be important in the striatum, where a balance between dopamine and ACh release ensures normal motor output,[4] and in the hippocampus and frontal cortex, where ACh has long been known to play a key role in the regulation of consciousness, learning and memory.[3] As ACh may be one of the major neurotransmitters affecting the action of anaesthetics, the pharmacological study of cholinergic mechanisms in anaesthesia is important.

Propofol (2,6-diisopropylphenol), a short-acting i.v. general anaesthetic, has been in clinical use since the 1980s and has been used widely for induction and maintenance of anaesthesia because of its versatility and favourable pharmacokinetics.[9] Propofol is believed to potentiate the inhibitory actions of the γ-aminobutyric acid A ($GABA_A$) receptor and its pharmacological mechanisms have been investigated in some detail. However, the molecular mechanisms by which the hypnotic effects of propofol occur are not fully understood.[9 10]

In this study, we examined the effects of propofol on ACh release from the rat frontal cortex, hippocampus and striatum in freely moving rats, and investigated the pharmacological mechanisms mediating the interaction of propofol with the $GABA_A$ receptor, using a brain microdialysis technique, coupled with a highly sensitive analytical method based on high performance liquid chromatography with electrochemical detection (HPLC-ECD).

Materials and methods

The study was approved by the Animal Welfare Committee of Yokohama City University School of Medicine. We studied adult male Sprague–Dawley rats (weighing 250–350 g). The animals were housed in cages at room temperature (22°C), maintained on a 12-h light–dark cycle (lights on 07:00–19:00 h) and were given free access to water and food. The animals

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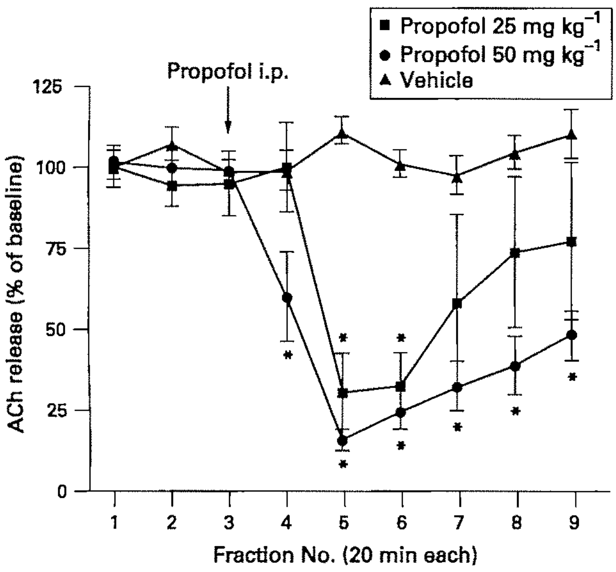

Figure 1 Effects of propofol 25 mg kg^{-1} (n=5) and 50 mg kg^{-1} (n=5) i.p. on acetylcholine (ACh) release from the rat frontal cortex. *P <0.05 compared with vehicle at the same times.

were anaesthetized with pentobarbital 40 mg kg^{-1} i.p. and placed in a stereotaxic apparatus (Model SR-6, Narisige Scient Instrument LAB., Japan). The skull was exposed and a guide cannula (CMA 10, Carnegie Medicine, Sweden) for penetration of a microdialysis probe was stereotaxically implanted into the right frontal cortex (coordinates taken from the bregma with the skull flat: A: 3.3 mm, L: 2.8 mm, V: 0.5 mm from the atlas of Paxinos and Watson[11]), the right hippocampus (coordinates from the bregma: A: −5.6 mm, L: 5.0 mm, V: 3.8 mm) and the right striatum (coordinates from the bregma: A: 1.0 mm, L: 3.0 mm, V: 4.0 mm), fixed with dental cement and fastened with four screws onto the skull of the rat. Microdialysis combined with HPLC-ECD in freely moving rats was performed, essentially as described previously,[3][4] at least 2 days after implantation of the guide cannula to allow for surgical recovery. The probe (CMA 11, Carnegie Medicine, Sweden) (2-mm long dialysis membrane for the right frontal cortex and 3-mm long dialysis membrane for the right hippocampus or striatum, od 0.24 mm, molecular weight cut-off=20 000 Da) was inserted into the guide cannula under diethyl ether anaesthesia on the day of the microdialysis experiment.

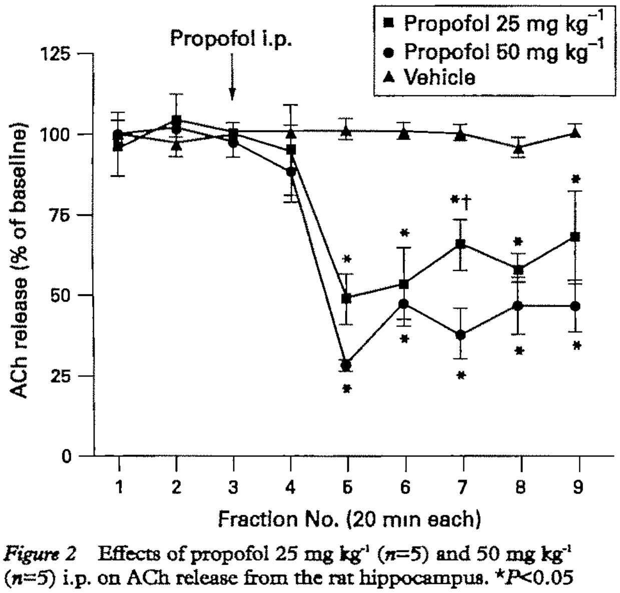

Figure 2 Effects of propofol 25 mg kg^{-1} (n=5) and 50 mg kg^{-1} (n=5) i.p. on ACh release from the rat hippocampus. *P<0.05 compared with vehicle at the same times; †P<0.05 compared with propofol 50 mg kg^{-1} at the same times.

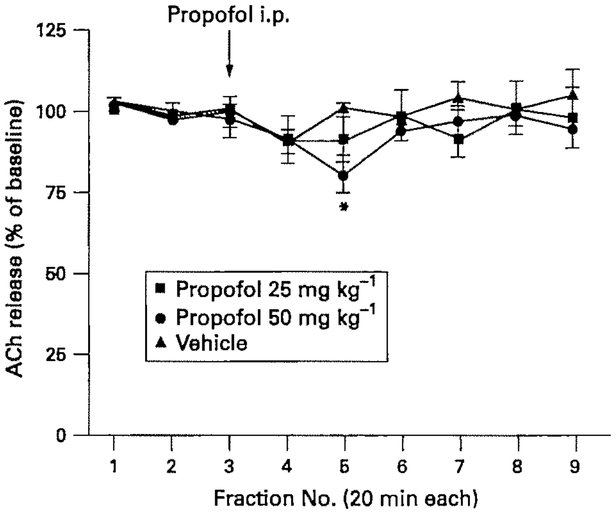

Figure 3 Effects of propofol 25 mg kg^{-1} (n=5) and 50 mg kg^{-1} (n=8) i.p. on ACh release from the rat striatum. *P<0.05 compared with vehicle at the same times.

Rats were allowed to move freely in a bowl-shaped cage. During the experiments, the microdialysis probes were perfused with Ringer's solution containing eserine sulphate 10 μmol litre^{-1} (Wako Pure Chemical Industries Ltd, Japan), an inhibitor of acetylcholine esterase (AChE), at a rate of 2.0 μl min^{-1} controlled by a micro infusion syringe pump (Model CMA 102, Carnegie Medicine, Sweden). Rats were pre-perfused with Ringer's solution for 120 min, and then every 20 min perfusate was collected in a chilled polyethylene tube containing 10 μl of ethylhomocholine 1 mmol litre^{-1}, an internal standard for HPLC determination.

The test drugs used were propofol (Zeneca Pharma., Japan) 25 and 50 mg kg^{-1} i.p. and (−)-bicuculline methylchloride (RBI, Natick, MA, USA), a GABA$_A$ receptor antagonist, 1 μmol litre^{-1} for local application or 1 μg kg^{-1} i.p. for systemic application. A new rat was used for each drug dose tested.

In our preliminary investigations, we confirmed the anaesthetic effects of propofol 10, 25 and 50 mg kg^{-1} i.p. in adult male Sprague–Dawley rats. Propofol 25 and 50 mg kg^{-1} produced loss of righting reflex and anaesthetic state within approximately 5–10 min after i.p. administration. A state of anaesthesia continued for approximately 60–90 min. A dose of propofol 10 mg kg^{-1} did not produce observable changes in behaviour in all rats. Therefore, we used doses of 25 and 50 mg kg^{-1} i.p. The i.p. route was favourable for experiments using freely moving rats because of ease of administration and reliability.[12][13]

After collecting three basal samples, propofol was administered i.p. Bicuculline 1 μmol litre^{-1} was dissolved in perfusate and given locally via the microdialysis probe from the start of experiments (local application), or bicuculline 1 μg kg^{-1} was given i.p. 20 min before propofol i.p. administration (systemic application). ACh release was measured by HPLC-ECD. Polymeric reversed-phase column (Eicom-pak AC-GEL, 6.0×150 mm, Eicom, Japan) was used for HPLC-ECD separation. An AC-Enzympak column (ACh esterase and choline oxidase-immobilized,

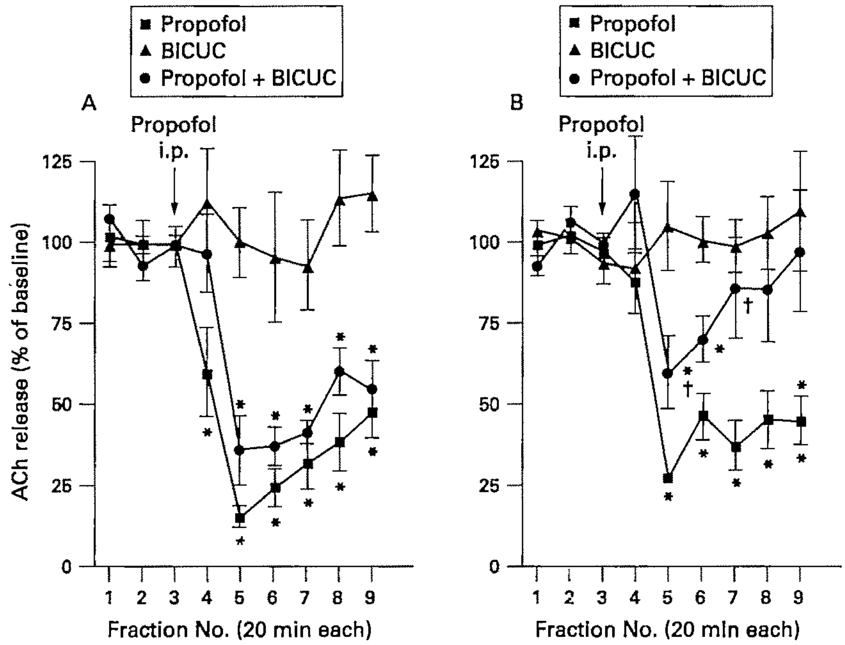

Figure 4 A: Effects of propofol 50 mg kg^{-1} i.p. (n=5) and bicuculline (BICUC) 1 μmol litre^{-1} (local perfusion) alone (n=5) or in combination (n=5), on ACh release from the rat frontal cortex. B: Effects of propofol 50 mg kg^{-1} i.p. (n=5) and bicuculline (BICUC) 1 μmol litre^{-1} alone (n=5) or in combination (n=5), on ACh release from the rat hippocampus. *P<0.05 compared with bicuculline alone; †P <0.05 compared with propofol 50 mg kg^{-1} i.p. alone.

Eicom, Japan) was used to convert ACh and choline to hydrogen peroxides, which were detected by an electrode (Model ECD-100, Eicom, Japan) at 450 mV. The mobile phase was phosphate buffer 100 mmol litre^{-1} (pH 8.5), containing tetramethylammonium chloride 65 mg litre^{-1} and decansulphonic acid sodium salt 200 mg litre^{-1}. The limit of sensitivity, defined as a signal-to-noise ratio >4, was 100 fmol (100 fmol/50 μl injection) for ACh. At the end of the experiments, the rats were killed using an overdose of diethyl ether, and the position of the probe in the brain was confirmed by visual examination. ACh recovery from the microdialysis probes was measured at the end of the experiment. *In vitro* ACh recovery (performed at 37°C) through 3-mm and 2-mm long dialysis membranes at a rate of 2 μl min^{-1} was mean 14.5 (SEM 0.5) % (n=15) and 11.0 (0.5) % (n=10), respectively.

Results are expressed as (mean (SEM)) percentage of basal ACh release. Basal release was obtained from the mean of three initial collections before administration of the test drugs. The significance of differences between mean values was determined by ANOVA with repeated measures, followed by Scheffe's F test for multiple comparisons. P<0.05 was accepted as significant.

Table 1 Peak effects of systemic (−)-bicuculline (BICUC) 1 and 10 μg kg^{-1} i p. and propofol 50 mg kg^{-1} i.p., alone or in combination, on ACh release from the rat frontal cortex. BICUC was given i.p. 20 min before propofol. Values are mean (SEM) percentage of baseline. *P<0.05 compared with bicuculline 1 μg kg^{-1}; †P<0.05 compared with propofol 50 mg kg^{-1} i.p. alone (ANOVA followed by Scheffe's F test for multiple comparisons)

Drug	Peak effects (% of baseline)
BICUC alone	
1 μg kg^{-1} i.p. (n=5)	105.3 (11.8)
10 μg kg^{-1} i.p. (n=5)	152.7 (22.6)*
Propofol 50 mg kg^{-1} i.p. (n=5)	15.8 (3.1)*
Propofol 50 mg kg^{-1} i.p. + BICUC 1 μg kg^{-1} i.p. (n=5)	50.4 (13.6)*†

Results

ACh release was stable over 120 min after commencing the perfusion. Baseline concentration of ACh in the frontal cortex, hippocampus and striatum in 20-min samples were 0.9 (0.1) pmol sample^{-1} (n=15), 1.8 (0.3) pmol sample^{-1} (n=15) and 14.8 (1.0) pmol sample^{-1} (n=18), respectively .

Figure 1 shows the effects of propofol on ACh release from the rat frontal cortex. Propofol 25 and 50 mg kg^{-1} i.p. decreased basal ACh release from the frontal cortex. Mean maximal decreases produced by propofol 25 and 50 mg kg^{-1} i.p. were 69% and 85%, respectively. Peak values of the mean decrease were measured in the second sample after i.p. injection (No. 5 fraction).

Figure 2 shows the effects of propofol on ACh release from the rat hippocampus. Propofol 25 and 50 mg kg^{-1} i.p. decreased ACh release from the hippocampus. Mean maximal decreases produced by propofol 25 and 50 mg kg^{-1} i.p. were 51% and 72% of basal levels, respectively. Peak values of the mean decrease were measured in the second sample after i.p. injection (No. 5 fraction).

Figure 3 shows the effects of propofol on ACh release from the rat striatum. In the rat striatum, propofol 25 mg kg^{-1} i.p. did not affect ACh release and 50 mg kg^{-1} i.p. produced slight inhibition of ACh release (19%).

In the hippocampus, local application of bicuculline 1 μmol litre^{-1} significantly antagonized the inhibitory effect of propofol 50 mg kg^{-1} i.p. (by 57.4%), while bicuculline 1 μmol litre^{-1} alone failed to alter ACh release (fig. 4B). However, in the rat frontal cortex, local application of bicuculline 1 μmol litre^{-1} did not significantly antagonize the inhibitory effect of propofol 50 mg kg^{-1} i.p. on ACh release (fig. 4A).

Table 1 shows the effect of systemic application of GABA$_A$ antagonist on ACh release from the frontal cortex. Although bicuculline 10 μg kg^{-1} i.p. increased ACh release to 152% of basal values in the frontal cortex, bicuculline 1 μg kg^{-1} i.p. failed to alter ACh release. Systemic pretreatment of bicuculline 1 μg kg^{-1} i.p. significantly antagonized the inhibitory effect of propofol 50 mg kg^{-1} i.p. (by 50.4 %), while bicuculline 1 μg kg^{-1} i.p. alone failed to alter ACh release.

Discussion

Brain microdialysis provides *in vivo* information on a variety of neurotransmitters in the extracellular space of the brain. In our microdialysis study, we investigated the effects of propofol on ACh release from various regions of the rat brain, including the frontal cortex, hippocampus and striatum.

Many reports have shown that general anaesthetics affect a variety of neurotransmitters in various rat brain regions.[7, 14, 15] In our previous study, we reported the inhibitory effects of pentobarbital on ACh release from the frontal cortex, hippocampus and striatum,[5, 6] which may imply that pentobarbital is a powerful depressant anaesthetic in all brain regions. Our present data showed that propofol decreased ACh release much more effectively in the frontal cortex or hippocampus than in the striatum, indicating that propofol has a "more selective" anaesthetic action than other depressant anaesthetics such as pentobarbital.

It is generally accepted that ACh in the striatum is an important neurotransmitter in the extrapyramidal motor neurone, regulating locomotion and movement.[16, 17] ACh in the hippocampus may be involved in cognitive functions such as memory and learning while ACh in the frontal cortex is concerned with concentration, attention span, initiative and spontaneity.[18, 19]

Propofol has gained widespread use because of the quality and speed of recovery. The magnitude and duration of impairment of psychomotor performance after propofol anaesthesia is distinctly less than that after barbiturate anaesthesia.[20] The results of our present study that propofol produced smaller effects on striatal ACh release compared with pentobarbital may explain the more rapid recovery of psychomotor function compared with barbiturate anaesthesia.[5]

Propofol is chemically unrelated to all other anaesthetic agents, such as barbiturates or benzodiazepines. Furthermore, the precise binding site of propofol is unknown, although it may be different from that of barbiturates or benzodiazepines.[21] It has been proposed that propofol could act by binding directly to the GABA$_A$ chloride channel or to the channel regulatory proteins.[22] Propofol has been shown to have a potent effect on GABA-activated chloride channels in rat brain[10, 23] and large effects on chloride conductance in *Xenopus* oocytes expressing mouse brain in mRNA.[24] The mechanism by which propofol potentiates GABA-mediated transmission is unlikely to involve inhibition of GABA reuptake, because the actions of muscimol and 3-aminopropanesulphonic acid (two structural analogues of GABA that are poor substrates for the GABA uptake systems) were also potentiated by propofol.[25] Bicuculline antagonizes GABA$_A$ receptors by competing with GABA for its binding sites and is known to induce convulsions. Schulz and Macdonald reported that barbiturates directly activate bicuculline-sensitive chloride conductance.[26]

As shown in figure 4B, our data demonstrated that propofol produced inhibitory effects on ACh release via "intra" hippocampal GABA$_A$ receptor mechanisms, at least in part in the rat hippocampus, which strongly supports the hypothesis that there may be a relationship between propofol and GABA$_A$ receptor mechanisms. However, as shown in figure 4A, local application of bicuculline did not significantly antagonize the inhibitory effects of propofol 25 and 50 mg kg^{-1} i.p. on ACh release in the rat frontal cortex. In contrast, systemic application of bicuculline 1 μg kg^{-1} i.p. (no effective dose) significantly antagonized the inhibitory effects of propofol 50 mg kg^{-1} i.p., as shown in table 1. Furthermore, the finding that systemic application of bicuculline 10 μg kg^{-1} i.p. alone increased ACh release from the frontal cortex indicates that ACh release from this region may be tonically inhibited by GABA$_A$ receptor activity. The reason why there is no effective action of locally applied bicuculline in the rat frontal cortex is unknown. One possibility is that "extra" frontal cortex GABA$_A$ receptor mechanisms may be involved in the inhibitory effects induced by propofol on ACh release from the rat frontal cortex. Further investigations are needed to elucidate the precise cellular mechanisms.

Studies of pentobarbital in primates have shown that it depresses metabolism in all brain areas.[27] On the other hand, in the clinical setting, using positron emission tomography, the effects of propofol on cerebral glucose metabolic rates showed that propofol did not uniformly depress metabolism throughout all brain regions.[28] Metabolism in the cortex was depressed more than that in subcortical regions, indicating that some regions were affected more than others.[26] These findings are comparable with ours; propofol produced significant inhibition of ACh release in the frontal cortex and hippocampus but only slight inhibition in the striatum *in vivo*. Therefore, propofol appears to have "more selective" anaesthetic actions than barbiturates. However, the precise pharmacological mechanisms and binding site of propofol are unknown.

In summary, propofol had a powerful depressant action on ACh release in the rat frontal cortex and hippocampus but not in the striatum, suggesting that propofol has a "locality selective" anaesthetic action. Furthermore, the inhibitory effects of propofol may be mediated by "extra" frontal cortex GABA$_A$ receptors in the frontal cortex, and "intra" hippocampal GABA$_A$ receptors in the hippocampus.

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Propofol and Intralipid interact with reactive oxygen species: a chemiluminescence study

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Summary

We have studied the ability of propofol and Intralipid to inhibit reactive oxygen species generated either by stimulated human leucocytes or cell-free systems using luminol chemiluminescence. Human leucocytes were stimulated by a chemotactic peptide, FMLP 1 µmol litre^{-1}, or by a phorbol ester, PMA (protein kinase C activator) 0.1 µmol litre^{-1}. In cell-free experiments, superoxide–hydrogen peroxide, hypochlorous acid or hydroxyl radical-induced chemiluminescence responses were initiated by xanthine 0.1 mmol litre^{-1} with xanthine oxidase 10 mu. ml^{-1}, NaOCl 70 µmol litre^{-1} and $FeSO_4$ 3 µmol litre^{-1}, respectively. Propofol with Intralipid, and to a lesser degree Intralipid alone, produced a concentration-dependent reduction in chemiluminescence from stimulated leucocytes. Similar attenuations were also observed using propofol with Intralipid on xanthine with xanthine oxidase-, HOCl- and ferrous iron-induced chemiluminescence. However, Intralipid produced a reduction only at high concentrations. Intralipid produced marked decreases in ferrous iron-induced chemiluminescence. This study suggests that propofol had a direct scavenging activity against HOCl, superoxide–hydrogen peroxide and hydroxyl radical in the concentrations used. These direct scavenging effects may contribute to the effect of propofol on human leucocyte chemiluminescence. (*Br. J. Anaesth.* 1998; **80**: 649–654)

Keywords: measurement techniques chemiluminescence, anaesthetics i.v. propofol; oxygen free radicals; blood leucocytes

Free radicals are believed to contribute to tissue injury associated with a wide range of chronic and acute diseases, such as acute lung injury, severe sepsis and multi-system organ failure. There is strong evidence that superoxide and hydrogen peroxide are intimately involved in initiating free radical damage and these oxidants lead to loss of cell integrity, tissue necrosis and organ failure.[1] Free radical scavengers, or antioxidants, represent an important component of the body's defences against such free radical mediated injury. Anaesthetic agents with antioxidant or free radical scavenging activity might be beneficial in some diseases where free radicals are believed to be involved. Moreover, most anaesthetic agents inhibit some aspects of immune function and this may be clinically important when prolonged infusions are used in the intensive care unit.[2]

Propofol (2, 6-diisopropylphenol) is a widely used i.v. anaesthetic agent with a rapid onset, short duration of action and rapid elimination.[3] It is related structurally to the commonly used phenolic antioxidants, namely butylated hydroxytoluene and α-tocopherol (vitamin E).[4,5] Propofol has demonstrated antioxidant activity against lipid peroxidation in human plasma,[4] rat liver mitochondria,[6,7] microsomes[6,8] and brain synaptosomes.[6] Propofol also attenuates ischaemia–reperfusion-induced lipid peroxidation in humans.[9] However, there are conflicting reports on the effects of propofol on leucocyte function. Although propofol has been shown to inhibit phagocytosis in one study,[10] it failed to produce significant effects on phagocytosis and respiratory burst activities at similar concentrations in another study.[11]

Chemiluminescence is used widely as a sensitive assay for monitoring free radicals and reactive oxygen metabolites from enzyme, cell or organ systems.[12–14] It is well established that polymorphonuclear (PMN) leucocytes, which are stimulated by a variety of both soluble and particulate stimuli, generate a series of oxygen-derived species. The initial product of oxygen reduction is superoxide ($^{\cdot}O_2^-$), generated during a respiratory burst. After $^{\cdot}O_2^-$ generation, other oxygen metabolites may be formed, including H_2O_2, $^1O_2$, $^{\cdot}OH$ and HOCl, the latter being formed in a reaction catalysed by myeloperoxidase.[1] Generation of reactive oxygen species and metabolites emits light which can be monitored by a variety of luminometers.[15] Light emission can be amplified markedly by luminol which measures a mixture of oxygen-derived species.[13,15]

The direct effects of propofol on oxygen-derived free radicals are unknown. As propofol is dissolved in 10% Intralipid for i.v. use and parenteral lipid emulsions have been reported to influence the cellular immune response,[16] the effects of Intralipid also need to be investigated. Therefore, in this study we investigated the effects of propofol and Intralipid on

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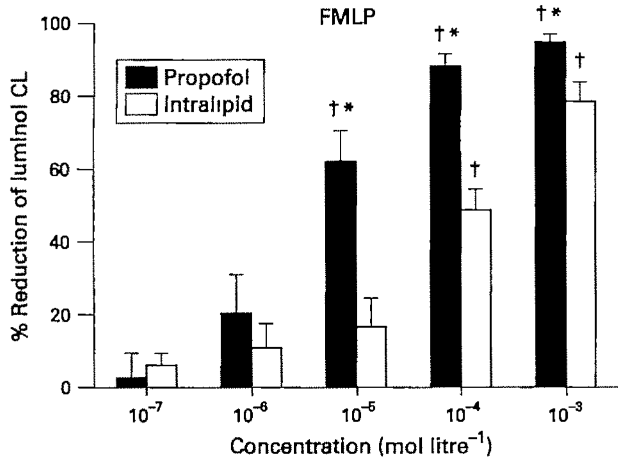

Figure 1 Concentration-dependent effects of propofol (n=4–7) and Intralipid (n=5–7) on FMLP 1 µmol litre^{-1}-induced luminol chemiluminescence (CL). Data are mean (SEM). *P<0.05 compared with corresponding Intralipid response; †P<0.05, significantly less than its control value.

chemiluminescence from stimulated leucocytes and examined direct scavenging activity in cell-free systems.

Materials and methods

ISOLATION AND SEPARATION OF LEUCOCYTES

Human venous blood was obtained from healthy volunteers and leucocytes were isolated according to methods described previously with slight modification.[14] Blood (9 ml) was obtained into tubes containing 3.8% sodium citrate 1 ml. Dextran was added and allowed to sediment at room temperature for 60 min. The leucocyte-rich supernatant was removed and centrifuged at 900 rpm for 20 min. Erythrocyte lysis was performed by washing cells with 0.2% NaCl for 30 s and mixing immediately with a double volume of 1.6% NaCl. Leucocytes were then centrifuged at 900 rpm for 15 min and the pellet resuspended in Hanks' buffered salt solution (HBSS) containing Ca^{2+} 1 mmol litre^{-1} (pH 7.4). Leucocytes were washed with HBSS three times. After leucocyte counting using a light microscope, cell yield was adjusted to 10^7 cells ml^{-1} (stock cell suspension) by adding HBSS. Cell viability was assessed by a Trypan blue exclusion test and more than 98% of the cells were found to be viable leucocytes (n=6). The stock cell suspension was stored at room temperature until use.

PMA- AND FMLP-INDUCED CHEMILUMINESCENCE

Stock leucocyte cell suspension (0.1 ml) was diluted with HBSS in a cuvette (total volume 1 ml) and luminol 20 µl (50 µmol litre^{-1}; final cuvette concentration) was added, producing a final cell yield of 10^6 cells ml^{-1}. Stimulant (phorbol 12-myristate 13-acetate (PMA) or N-formyl-methionyl-leucyl-phenylalanine (FMLP)) was then added to yield final cuvette concentrations of 10^{-7} mol litre^{-1} and 10^{-6} mol litre^{-1}, respectively. Luminol chemiluminescence was measured at 37°C using a chemiluminometer (Bio-Orbit 1250 Luminometer, Turku, Finland). The chemiluminescence produced was measured continuously and recorded on a computer using the Luminometer 1250 program (version 1.12, Bio-Orbit).

XANTHINE–XANTHINE OXIDASE-INDUCED CHEMILUMINESCENCE

Superoxide and hydrogen peroxide were generated enzymatically by the xanthine–xanthine oxidase reaction system.[13 14] In order to characterize xanthine–xanthine oxidase-induced chemiluminescence, 0.9 ml of phosphate-buffered saline (PBS: KH_2PO_4 10 mmol litre^{-1} and NaCl 150 mmol litre^{-1}, pH 7.4) were mixed with luminol 0.1 ml (250 µmol litre^{-1}; final cuvette concentration) in a cuvette. After further addition of 10 µl of xanthine 0.1 mmol litre^{-1}, 25 µl of xanthine oxidase 10 mu. ml^{-1} was injected into the cuvette, and the chemiluminescence produced was measured continuously for 5 min.

HOCL-INDUCED CHEMILUMINESCENCE

HOCl was prepared as described previously by Vissers and colleagues.[17] NaOCl was diluted with PBS and the pH of the solution readjusted to 7.4 immediately before addition to the chemiluminescence cuvette. At this pH, the solution contains approximately 1:1 HOCl and OCl^- and is subsequently referred to as HOCl. HOCl 70 µmol litre^{-1} was injected into the HBSS and luminol 250 µmol litre^{-1} mixture to induce chemiluminescence.

FERROUS IRON-INDUCED CHEMILUMINESCENCE

Hydroxyl radicals were generated by addition of ferrous iron to the buffer solution, as described previously by Green, Bennett and Nelson.[5] Ferrous iron reduces molecular oxygen to superoxide radical, which in turn dismutates to hydrogen peroxide. Further reduction of H_2O_2 by Fe^{2+} produces the highly reactive hydroxyl radical. Freshly prepared $FeSO_4$ 3 µmol litre^{-1} was injected into the PBS and luminol 250 µmol litre^{-1} mixture, and chemiluminescence was recorded continuously for 5 min.

EXPERIMENTAL PROCEDURE

The effects of various concentrations of propofol, Intralipid or enzyme inhibitors were examined by addition before the stimulant. In PMA-stimulated leucocytes, the effects of propofol and Intralipid were also studied when the chemiluminescence signal reached a peak. Duplicate assays were performed in all experiments. Results were calculated as peak chemiluminescence or as a percentage of peak chemiluminescence, and expressed as mean (SEM). n refers to the number of individual volunteers (for leucocyte experiments) and number of experiments (for cell-free assays). Comparisons of the differences between mean values were performed using an unpaired Student's t test. Analysis of variance (ANOVA) was used to assess the observed differences in chemiluminescence between concentrations. If significant differences were detected by ANOVA, individual means were compared with control using a Dunnett test. Differences were considered to be statistically significant when P<0.05.

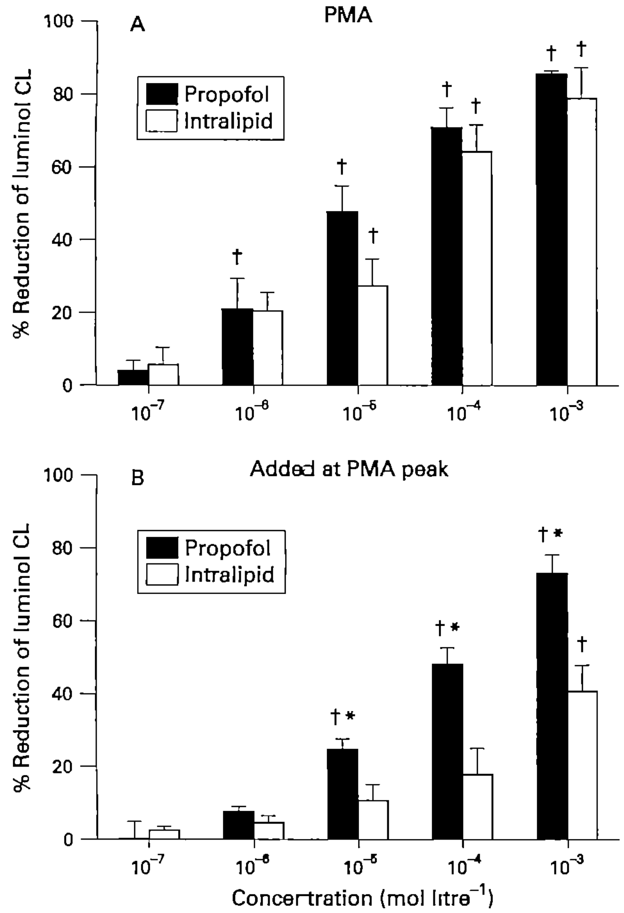

Figure 2 Concentration-dependent effects of propofol (n=6–7) and Intralipid (n=7) on PMA 0.1 μmol litre^{-1}-induced luminol-enhanced chemiluminescence (CL) when added before PMA (A) or at the peak of the PMA response (n=4–6 for propofol and n=5–6 for Intralipid) (B). Data are mean (SEM). *$P<0.05$ compared with corresponding Intralipid values; †$P<0.05$, significantly less than its control value.

MATERIALS

Commercially available preparations of propofol (Diprivan, Zeneca Ltd, Macclesfield, Cheshire, UK) and Intralipid (Lipovenös 10%, Fresenius AG, Germany) were used and diluted with saline. Intralipid 10% is the vehicle for commercially available propofol, and contains 10% soybean oil, 2.5% glycerol and 1.2% purified egg phosphatide. PMA and FMLP were dissolved in ethyl alcohol and fresh dilutions were made by PBS before use. Luminol was prepared daily in NaOH 2 mol litre^{-1} (2.5%) and diluted with PBS. Xanthine (sodium salt) and xanthine oxidase (grade I, from buttermilk) were dissolved in distilled water. $FeSO_4$ was prepared in distilled water before use. Superoxide dismutase (from bovine erythrocytes), catalase (from bovine liver), D-mannitol and NaOCl were dissolved in PBS before use. All chemicals were purchased from Sigma Chemical Co. (St Louis, MO, USA).

Results

Concentrations of 10 mu. ml^{-1}, 70 μmol litre^{-1} and 3 μmol litre^{-1} were selected for xanthine oxidase, HOCl and $FeSO_4$, respectively, and generated chemiluminescence peaks (1898 (117) mV (n=11) for xanthine–xanthine oxidase, 1855 (45) mV (n=22) for HOCl and 2064 (75) mV (n=34) for $FeSO_4$) were found to be comparable with that produced by PMA 0.1 μmol litre^{-1} in leucocytes (2053 (208) mV (n=15)). Both receptor-mediated (FMLP) and non-receptor-mediated (PMA, a protein kinase C activator) stimulants were used for activation of leucocytes.

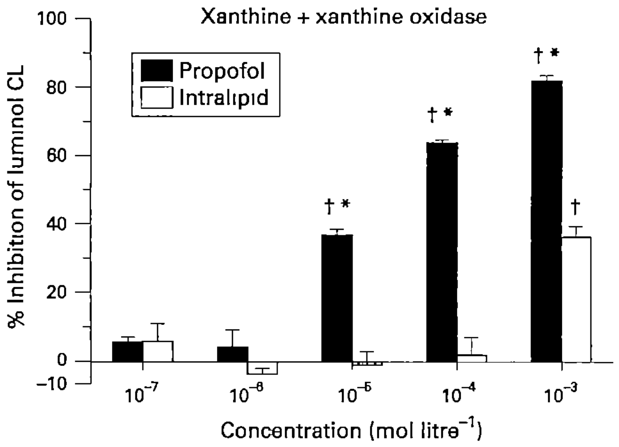

Figure 3 Concentration-dependent effects of propofol (n=6–9) and Intralipid (n=5–10) on xanthine 0.1 mmol litre^{-1} with xanthine oxidase 10 mu ml^{-1}-induced luminol chemiluminescence (CL). Data are mean (SEM). *$P<0.05$ compared with corresponding Intralipid response; †$P<0.05$, significantly less than its control value

EFFECTS OF PROPOFOL WITH INTRALIPID AND INTRALIPID ALONE ON LUMINOL CHEMILUMINESCENCE IN LEUCOCYTES

In luminol chemiluminescence, FMLP 1 μmol litre^{-1} induced response (1620 (162) mV, n=6) was depressed by either propofol with Intralipid or an equivalent volume of Intralipid in a concentration-dependent manner. The Intralipid concentrations used in this study were 1.78×10^{-4} to 17.8 μl ml^{-1}, which were carrying corresponding concentrations of propofol of 0.01 μmol litre^{-1} to 1 mmol litre^{-1}, respectively. There was a marked reduction in FMLP-induced luminol chemiluminescence by the combination of propofol and Intralipid, with an IC_{50} value of 4.6 μmol litre^{-1} (fig. 1). To exclude the possibility that the inhibitory effect of propofol and Intralipid on luminol chemiluminescence was specific to FMLP, the effects of these drugs were also tested on PMA-activated leucocytes. Propofol with Intralipid produced concentration-dependent depression of luminol chemiluminescence in PMA-activated leucocytes when added before PMA, with an IC_{50} value of 7 μmol litre^{-1} (fig. 2). Propofol with Intralipid started to decrease PMA-induced luminol chemiluminescence at 1 μmol litre^{-1} (21 (8) %, n=6). At the concentrations tested, maximum reduction with the propofol and Intralipid combination was observed at 1 mmol litre^{-1} (86 (1) %, n=7). Intralipid caused significant attenuation similar to that produced by propofol with Intralipid (79 (9) %, n=7 at 17.8 μl ml^{-1}) (fig. 2A). Addition of propofol with Intralipid and Intralipid alone at the peak of chemiluminescence also produced concentration-dependent reduction in PMA-activated leucocytes. This inhibition was similar to that seen by addition of propofol with Intralipid before the stimulant (73 (5) %, n=4, at 1 mmol litre^{-1}). In contrast, Intralipid produced only a 40 (8) % (n=6) decrease at 17.8 μl ml^{-1} on PMA-induced luminol chemiluminescence (fig. 2B).

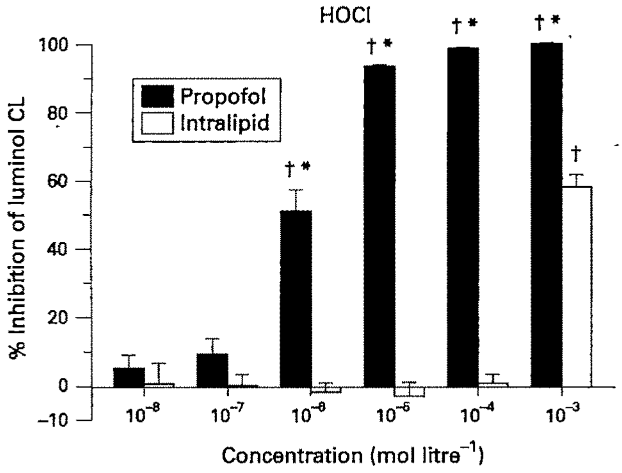

Figure 4 Concentration-dependent effects of propofol (n=6–9) and Intralipid (n=5–9) on HOCl 70 µmol litre^{-1}-induced luminol-enhanced chemiluminescence (CL). Data are mean (SEM). *$P<0.05$ compared with corresponding Intralipid values; †$P<0.05$, significantly less than its control value.

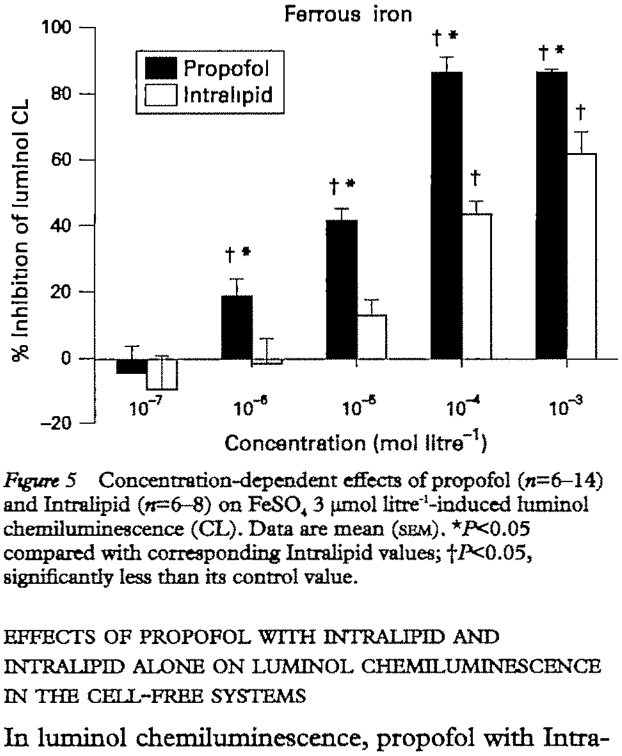

Figure 5 Concentration-dependent effects of propofol (n=6–14) and Intralipid (n=6–8) on $FeSO_4$ 3 µmol litre^{-1}-induced luminol chemiluminescence (CL). Data are mean (SEM). *$P<0.05$ compared with corresponding Intralipid values; †$P<0.05$, significantly less than its control value.

EFFECTS OF PROPOFOL WITH INTRALIPID AND INTRALIPID ALONE ON LUMINOL CHEMILUMINESCENCE IN THE CELL-FREE SYSTEMS

In luminol chemiluminescence, propofol with Intralipid inhibited xanthine–xanthine oxidase-induced responses in a concentration-dependent manner, with an IC_{50} value of 18.5 µmol litre^{-1} (fig. 3). At the concentrations tested, maximum inhibition was recorded at 1 mmol litre^{-1} (82 (2) %, n=9). However, Intralipid was only effective at the highest concentration (17.8 µl ml^{-1}) and produced 36 (3) % (n=8) inhibition (fig. 3).

HOCl 70 µmol litre^{-1}-induced luminol chemiluminescence was also inhibited by the combination of propofol and Intralipid in a concentration-dependent manner. Inhibition was observed at 1 µmol litre^{-1} (51 (6) %, n=7) and there was almost complete inhibition at propofol 0.1 mmol litre^{-1} (99 (0.1) %, n=9) with an IC_{50} value of 1 µmol litre^{-1}. While Intralipid had no effect at 1.78 µl ml^{-1} (1 (3) %, n=9), it produced 58 (4) % (n=8) inhibition at 17.8 µl ml^{-1} (fig. 4).

Propofol with Intralipid and Intralipid alone produced concentration-dependent inhibition of $FeSO_4$ 3 µmol litre^{-1}-induced chemiluminescence response. There was 86 (0.8) % (n=14) and 61 (7) % (n=7) suppression by propofol 1 mmol litre^{-1} and Intralipid 17.8 µl ml^{-1}, respectively. Inhibition with propofol–Intralipid (IC_{50}=8.2 µmol litre^{-1}) was more marked compared with Intralipid alone (fig. 5). In order to determine the reactive oxygen species responsible for ferrous iron-induced chemiluminescence, superoxide dismutase 50 iu ml^{-1}, catalase 500 iu ml^{-1} and the hydroxyl radical scavenger, mannitol 100 mmol litre^{-1}, were used. Ferrous iron-induced chemiluminescence was inhibited significantly by superoxide dismutase and catalase by 88 (1) % (n=7) and 66 (3) % (n=5), respectively. Ferrous iron-induced chemiluminescence was also inhibited markedly by mannitol (83 (2) %, n=5) showing that $^{\cdot}OH$ was generated and involved in the chemiluminescence response (data not shown).

Discussion

Binding of FMLP to its specific membrane receptors on phagocytes stimulates NADPH oxidase, the enzyme responsible for production of superoxide radical, mainly by activation via phospholipase C and increase in Ca^{2+} influx. However, PMA binds directly to protein kinase C and activates superoxide formation in leucocytes at low intracellular Ca^{2+} concentrations.[18] In this study, propofol and Intralipid reduced chemiluminescence generated by FMLP- and PMA-activated leucocytes, suggesting that reduction occurs in a non-receptor mediated way. This attenuation does not seem to require preincubation as propofol and Intralipid were introduced just before the stimulant. Additionally, in PMA-stimulated leucocytes, propofol and Intralipid also reduced chemiluminescence when added at the peak, implying direct interaction with reactive oxygen species. Previous studies showed that free radical release from activated leucocytes was impaired after *in vitro* propofol and Intralipid exposure.[10 19–21] At anaesthetic concentrations, propofol produced significant inhibition of PMA-induced respiratory burst in human neutrophils measured by flow cytometry.[10] The effect of the vehicle of propofol has been shown to be similar to that of propofol, implying that suppression of respiratory burst of neutrophils by propofol may be caused partly by this lipid and is unrelated to cell death.[10] Clinically relevant concentrations of propofol suppressed phagocytosis, neutrophil polarization and killing of bacteria in human PMN leucocytes, while Intralipid impaired phagocytosis.[20 22] However, in another study, propofol produced no significant depression of phagocytosis and hydrogen peroxide production of human PMN leucocytes incubated for 1 h with i.v. anaesthetics at clinically relevant concentrations measured by flow cytometry.[11]

There is disagreement on the effect of Intralipid on leucocyte function. Both inhibitory[10] and stimulatory[22 23] responses have been reported. Previous studies demonstrated that neutrophils preincubated with Intralipid exhibited diminished chemotactic responses and inhibited neutrophil bactericidal activity, superoxide generation, phagocytosis[16 24] and T-cell mediated immunity *in vitro*.[23] In a previous study, it has been shown that 10% Intralipid augmented neutrophil polarization,[22] which is in contrast with another study, where Intralipid suppressed neutrophil chemotaxis.[23] Additionally, polyunsaturated fatty acids can be incorporated rapidly into cell membranes[26] and increase membrane rigidity.[27] These changes in membrane structure may provide an explanation for the decrease in chemiluminescence response. There is concern about the potential for increased serum lipid concentrations, particularly in patients receiving prolonged infusions.

Propofol has been demonstrated to delay significantly the onset of lipid peroxidation compared with Intralipid.[4] The inhibitory effects of propofol on malondialdehyde production in rat liver mitochondria, microsomes and brain synaptosomes indicate that its antiperoxidative action is comparable with that of butylated hydroxytoluene.[6] Propofol also inhibited lipid peroxidation initiated by hydrogen peroxide[28] or hydroxyl, ferryl and oxo-ferryl radicals.[29] It is assumed that propofol behaves as a chain breaking antioxidant *in vitro*, and scavenges lipid peroxyl radicals by a process of hydrogen abstraction to form the relatively stable propofol phenoxyl radical.[4,7] In addition to these effects, we have shown recently that propofol also scavenges peroxynitrite, a potent toxic metabolite generated from the interaction of nitric oxide and superoxide.[30] Intralipid has been shown to have no effect on lipid peroxidation[4] but suppresses the effectiveness of propofol in scavenging free radicals.[5]

Our results showed that propofol significantly inhibited chemiluminescence generated by superoxide radical–hydrogen peroxide, hydroxyl radical and HOCl. However, the most potent inhibitory effect of propofol was for HOCl. To our knowledge, this is the first experimental evidence that propofol is a potent scavenger of HOCl. Intralipid, however, caused marked inhibition of hydroxyl radical generation and this effect is likely to be responsible for the inhibition seen in PMA- and FMLP-activated leucocytes. Our results suggest that propofol exerts scavenging activity on superoxide–hydrogen peroxide, hydroxyl radical and HOCl in addition to the previously shown organic, organoperoxyl radical species[5] and peroxynitrite.[30] Our results disagree with the studies demonstrating that propofol does not react with oxygen centred radicals (superoxide, hydrogen peroxide and hydroxyl radical).[4,5] This discrepancy is probably because of the different laboratory techniques used (chemiluminescence *vs* electron spin resonance (ESR) spectroscopy or illumination of riboflavin and measurement of degradation products of propofol). Failure to demonstrate a hydroxyl radical scavenging effect of propofol is probably because of the reaction of hydroxyl radical with the large concentrations of acetone as a solvent in ESR studies.[4]

The clinical consequences of inhibition of membrane lipid peroxidation and direct free radical scavenging activity of propofol have not been well documented in patients. At anaesthetic concentrations, propofol produced 50% inhibition of neutrophil polarization and complete inhibition was attained with higher concentrations.[22] In another *in vitro* study, Jensen, Dahlgren and Eintrei[25] found a decrease in chemotaxis of human neutrophils produced by propofol after zymosan stimulation. Clinically relevant concentrations of propofol also depressed migration of human PMN leucocytes.[25] Therefore, inhibition of the immune response may have serious effects if propofol and Intralipid are administered continuously to patients with known infection or to immunocompromised patients, and may increase the risk of postoperative infections. In contrast, in many clinical situations, endogenous antioxidant defence systems may be diminished, making cell membranes even more vulnerable to oxidative stress and causing an increase in lipid peroxidation. Thus during anaesthesia for cardiac, vascular and transplantation surgery, or during sedation of the critically ill, in patients undergoing artificial ventilation in the intensive care unit with sepsis or severe burns, propofol offers theoretical advantages by scavenging reactive oxygen species and metabolites, and inhibiting lipid peroxidation.

In summary, we found that propofol with Intralipid suppressed respiratory burst in a concentration-dependent manner in leucocyte experiments. As Intralipid per se produced a less marked decrease, some of the effects of propofol on respiratory burst may be attributed to its lipid vehicle. Although propofol was proposed as a scavenger of organic radicals rather than superoxide and hydroxyl radicals, our results showed that propofol had direct scavenging activity against superoxide radical–hydrogen peroxide, hydroxyl and HOCl. Therefore, the direct scavenging activity of propofol may contribute to the reduction in luminol chemiluminescence in PMA-activated leucocytes. Our results provide experimental support for investigating the potential benefit of using propofol as an anaesthetic agent in patients presenting pathologies associated with free radical reactions.

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Relaxant effects of propofol on human omental arteries and veins

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Summary

We have investigated the relaxant effects of propofol on smooth muscle tension in human omental arteries and veins to determine if endothelium-related mechanisms are involved. Isolated vessel segments were precontracted with endothelin-1 and propofol was added cumulatively (10^{-7}–10^{-4} mol litre^{-1}). In both artery and vein segments, propofol induced relaxation, which was not dependent on an intact endothelium. Relaxation was reduced when the extracellular K^+ concentration was increased and in the presence of tetraethylammonium chloride (TEA). In intact segments, N-nitro-L-arginine methyl ester (L-NAME), indomethacin, glibenclamide, 4-aminopyridine, clotrimazole and atropine did not affect the concentration–response curve of propofol. This indicates that propofol relaxes human omental arteries and veins in an endothelium independent manner, and that hyperpolarization caused by activation of the K^+ channel, BK_{Ca}, may be involved. (*Br. J. Anaesth.* 1998; **80**: 655–659)

Keywords: anaesthetic i.v., propofol; arteries, omental; veins, omental

Propofol anaesthesia often causes undesirable hypotension. The vascular effects of propofol are poorly understood, but it seems to affect both the arterial and venous circulation, resulting in a reduction in systemic vascular resistance[1–5] and an increase in capacitance,[6 7] respectively.

Propofol reduces vascular smooth muscle tone both directly[6 8 26]; and indirectly,[9–11] for example via effects on sympathetic activity. Relaxation of vascular smooth muscle may be achieved by several mechanisms. Endothelium-dependent relaxation includes nitric oxide formation,[12] prostanoid synthesis,[13] and release of endothelium-derived hyperpolarizing factors activating smooth muscle potassium (K^+) channels.[14] Endothelium-independent relaxation includes altering the availability of free cytosolic calcium, for example via effects on voltage-gated Ca^{2+} channel activity.[15]

Several studies have attempted to explain the complex actions of propofol. Propofol has been shown to relax vascular smooth muscle in both an endothelium-dependent[16–20] and independent manner.[21–24] Various mediators for the action of propofol have been suggested. Formation of nitric oxide or prostanoids, or both,[16 20–25] have been shown to be involved. Propofol has also been suggested to alter free cytosolic calcium concentrations in vascular smooth muscle.[19 21 22 24 26–28] It seems that propofol may interact at several cellular targets, thereby causing relaxation of vascular smooth muscle.

The aim of this study was to investigate the direct relaxant effects of propofol on human vascular smooth muscle and to determine if endothelium-related mechanisms are involved. Experiments were performed on intact and endothelium-denuded vessel segments and in the presence or absence of inhibitors of the synthesis or action, or both, of nitric oxide, prostanoids and endothelium-derived hyperpolarizing factors.

Materials and methods

The following compounds were used: propofol (Diprivan, Zeneca); 10% Intralipid (Pharmacia Upjohn); 9,11-dideoxy-11α,9α-epoxy-methanoprostaglandin $F_{2\alpha}$ (U46619, Sigma, thromboxane A_2 analogue); substance P acetate (SP, Sigma); endothelin-1 (ET-1, Sigma); N-nitro-L-arginine methyl ester hydrochloride (L-NAME, Sigma, inhibitor of nitric oxide synthase); sodium-indomethacin (Confortid, Dumex, inhibitor of cyclo-oxygenase); tetraethylammonium chloride (TEA, Sigma, non-selective inhibitor of K^+ channels, with some preference for the high conductance Ca^{2+}-sensitive K^+ channel, BK_{Ca}); glibenclamide (Sigma, inhibitor of ATP-sensitive K^+ channels, K_{ATP}); 4-aminopyridine (4-AP, Sigma, inhibitor of voltage-sensitive K^+ channels, K_V); clotrimazole (Sigma, inhibitor of the cytochrome P450 system and the intermediate conductance Ca^{2+}-activated K^+ channels, I_{KCa}); atropine (Atropin, NM Pharma, antagonist of muscarinic receptors); and dimethyl sulphoxide (DMSO, Sigma). Sodium indomethacin was dissolved in a phosphate buffer and glibenclamide and clotrimazole were dissolved in DMSO. All other compounds were dissolved in distilled water. The Krebs–Ringer solution (KRS) contained (mmol litre^{-1}): Na^+ 143, K^+ 4.6, Cl^- 126.4, Ca^{2+} 2.5, HCO_3^- 25.0, Mg^{2+} 0.79, SO_4^{2-} 0.79, $H_2PO_4^-$ 1.2, glucose 5.5 and EDTA 0.024. EDTA was added to the solution to chelate trace metal ions and minimize oxidation of the other compounds used. The lipid KRS contained KRS with 0.2% of 10% Intralipid (that is g litre^{-1}): soy bean oil 0.178, egg phospholipid 0.021 and glycerol 0.04.

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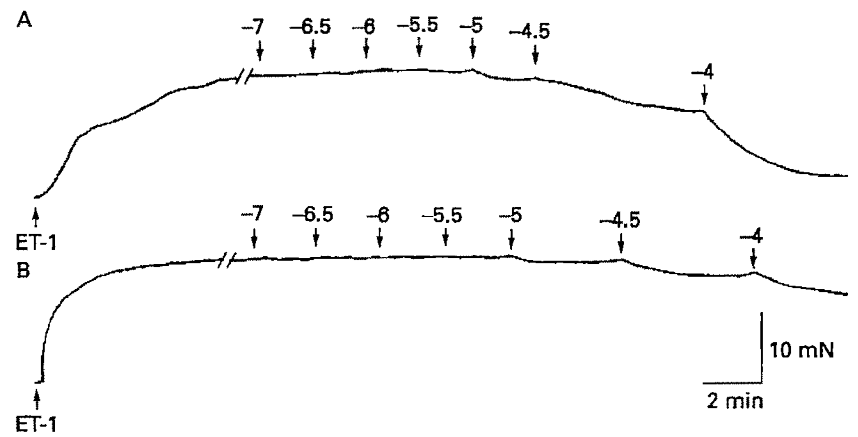

Figure 1 Isometric tension tracing in an isolated human omental artery (A) and vein (B) segment during cumulative addition of propofol ($\log_{10}$ mol litre^{-1}), after precontraction with endothelin-1 (ET-1).

The study was approved by the Ethics Committee, University of Lund. Macroscopically normal segments of human omental arteries and veins were obtained from 22 patients aged 36–88 (median 69) yr undergoing abdominal surgery. Patients with endocrine tumours, abdominal infections and previous radiotherapy were excluded. The male/female ratio was 0.7. Experiments were performed within 1–24 h. Vessel segments, after being dissected free from fat and connective tissue, were stored in aerated KRS at 4°C. There was no correlation between responses and storage time.

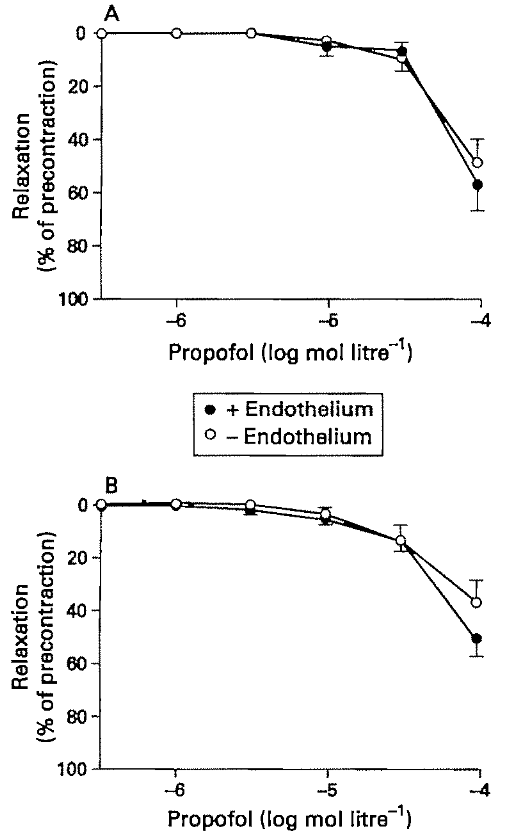

Figure 2 Concentration–response curves for propofol in human omental artery (A) and vein (B) segments precontracted with endothelin-1 (ET-1) in the presence or absence of an intact endothelium. Removal of endothelium did not affect the response to propofol. Values are mean (SEM), n=5–6.

MEASUREMENT OF CHANGES IN ISOMETRIC TENSION

Vessels with an outer diameter of 0.5–1.0 mm were cut into 2–4-mm long ring segments. The segments were placed in 2-ml tissue baths on two L-shaped hooks, one of which was attached to a Grass FTO3C force-displacement transducer for isometric measurement of tension. Vessel tension was recorded on a Grass polygraph model 7b. The baths were thermostatically maintained at 37°C and contained lipid KRS (see composition above), which was aerated continuously with 88.5% oxygen and 11.5% carbon dioxide, to give approximate values of pH 7.4, $P\text{CO}_2$ 5.0 kPa and $P\text{O}_2$ 40 kPa. With the use of lipid KRS, it was possible to maintain a constant lipid concentration in the baths, even when different concentrations of propofol were added.

Vessel segments were stretched gradually to a resting tension of 6 mN during an equilibration period of 60–90 min to obtain the optimal tension level.[29] After the equilibration period, KCl 90 mmol litre^{-1} was added to the baths. When the resulting contraction had reached a plateau, the lipid KRS was changed three times within 10 min, during which tension returned to baseline. KCl 90 mmol litre^{-1} was then added 1–2 times, each time followed by wash-out until consistent contractions were elicited. With this procedure, endothelium stays functionally and anatomically intact.[30]

Experimental procedure

In the first series of experiments, we investigated the endothelium dependency of the action of propofol. The endothelium of one artery and one vein segment from six patients was removed by gentle injection of the oxygen–carbon dioxide gas mixture through the vessel lumen for 5 min.[31] To confirm that the endothelium had been removed successfully, substance P (SP), an agent which is totally dependent on a functional endothelium for its action in these preparations,[29] was added to vessel segments precontracted with the thromboxane A_2 analogue U46619 (10^{-8}–3×10^{-7} mol litre^{-1}). SP caused no response in endothelium-denuded vessel segments but caused relaxation in control vessel segments. Vessel segments were rinsed several times after addition of SP. Then ET-1 1–3×10^{-9} mol litre^{-1} was added. This

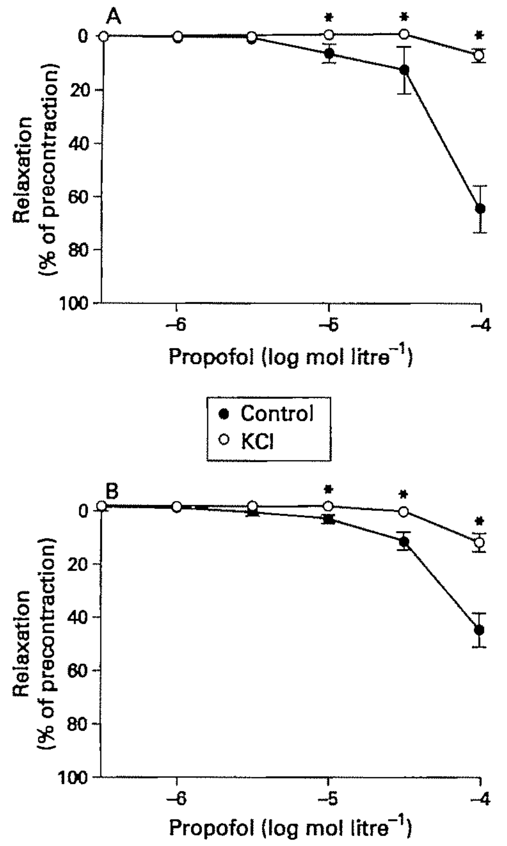

Figure 3 Concentration–response curves for propofol in human omental artery (A) and vein (B) segments precontracted with endothelin-1 (ET-1) in the presence or absence (control) of KCl 30 mmol litre^{-1}. Propofol-induced relaxation was reduced by KCl. The Wilcoxon signed rank test was used (*$P<0.05$). Values are mean (SEM), $n=7$.

concentration corresponds to the EC$_{50}$ value in these preparations.[32] ET-1 was first added at 1×10^{-9} mol litre^{-1}. If no contraction was elicited, the concentration was increased stepwise until the segments contracted. Within 10 min, ET-1-induced contraction reached a plateau. Pilot experiments had shown that this contraction remained constant without fade for at least 30 min. When a stable level of tension had been reached, propofol was added cumulatively in 0.5 log$_{10}$ units (10^{-7}–10^{-4} mol litre^{-1}) and the resulting relaxation measured. Propofol was added in a cumulative manner to assess any potential concentration dependency of the responses and to construct concentration–response curves. Each concentration of propofol was present in the bath for 2 min or until a stable tension was reached after relaxation. The cumulative concentration–response experiments with propofol took 15–20 min and were therefore performed on vessels with a stable ET-1 contraction.

In the second series of experiments, we determined by which mechanisms propofol-induced relaxation was mediated. The effect of propofol on segments precontracted with ET-1 was investigated in the presence or absence of indomethacin 10^{-5} mol litre^{-1}, L-NAME 3×10^{-4} mol litre^{-1}, KCl 30 mmol litre^{-1}, TEA 10^{-3} or 10^{-2} mol litre^{-1}, glibenclamide 10^{-5} mol litre^{-1}, 4-AP 10^{-3} mol litre^{-1}, clotrimazole 10^{-5} mol litre^{-1} or atropine 10^{-6} or 10^{-5} mol litre^{-1}. Control experiments were performed simultaneously on separate segments from the same patient, generating paired data with or without treatment. To exclude an effect of the solvent DMSO used in the glibenclamide and clotrimazole experiments, control experiments were also performed in the presence of DMSO at the equivalent concentration (141 mmol litre^{-1}) alone. The vasoactive compounds were added to the organ baths 10 min before addition of ET-1.

STATISTICAL ANALYSIS

When similar experiments were performed on more than one segment from the same patient, the mean for each patient was calculated before presentation and statistical analysis. The number of patients is indicated by "n". Values are expressed as mean (SEM). The Wilcoxon signed rank test was used for statistical evaluation. $P<0.05$ was considered statistically significant and only significant differences are mentioned in the text.

Results

Propofol induced concentration-dependent relaxation in both artery and vein segments (fig. 1A, B). With propofol 10^{-4} mol litre^{-1}, relaxation was 35–70% of precontraction values; this represented between- rather than within-patient variation. Removal of the endothelium did not affect the concentration–response curve of propofol (fig. 2A, B).

Precontraction induced by ET-1 or the response to propofol was not affected by indomethacin (artery $n=6$, vein $n=5$), L-NAME (artery $n=7$, vein $n=8$), glibenclamide (artery $n=5$, vein $n=5$), 4-AP (artery $n=7$, vein $n=7$), clotrimazole (artery $n=6$, vein $n=5$), atropine (artery $n=5$, vein $n=5$) or the solvent DMSO (artery $n=4$, vein $n=4$) (data not shown).

An increase in extracellular KCl concentration did not affect precontraction induced by ET-1, but reduced the relaxation induced by propofol in both artery and vein segments (fig. 3A, B).

TEA 10^{-3}–10^{-2} mol litre^{-1} did not affect precontraction induced by ET-1. TEA 10^{-2} mol litre^{-1} reduced propofol-induced relaxation in both artery and vein segments. At TEA 10^{-3} mol litre^{-1}, propofol-induced relaxation was inhibited only at the highest concentration of propofol and only in veins (fig. 4A, B).

Discussion

We have shown that propofol produced concentration-dependent relaxant effects on human omental arteries and veins. The propofol concentrations needed were high and exceeded those seen clinically. Clinically relevant plasma concentrations of propofol have been estimated to be 1–5×10^{-5} mol litre^{-1}.[33, 34] However, *in vitro* and *in vivo* concentrations are not easy to compare, as the *in vivo* situation cannot be mimicked completely. Several factors may interfere, such as plasma protein binding and lipid solubility, two factors which are both reported to be important for propofol.[25, 35] Hence the clinical relevance of our findings remains to be determined. The poor water solubility of propofol requires the use of a lipid solvent for its administration. In this study, we chose 10% Intralipid as it is the vehicle used clinically. The observed effects of propofol cannot be a result of 10% Intralipid as the equivalent concentration of Intralipid was always present in the control organ baths.

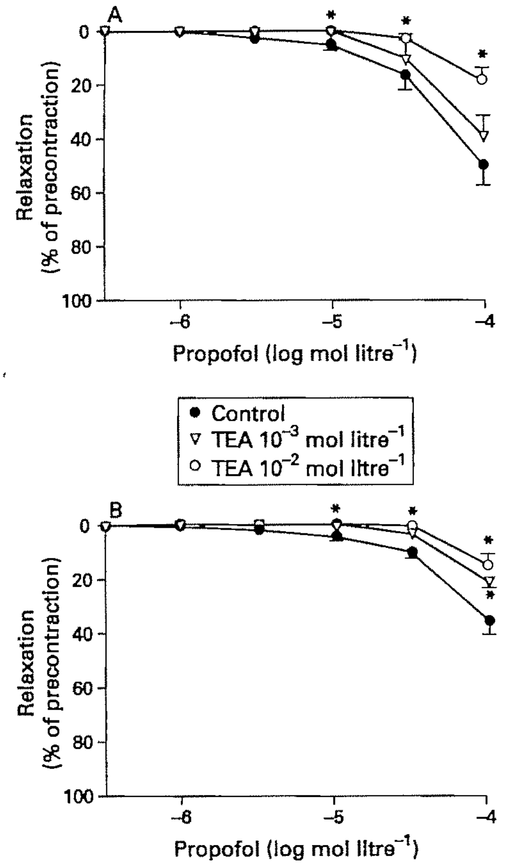

Figure 4 Concentration–response curves for propofol in human omental artery (A) and vein (B) segments precontracted with endothelin-1 (ET-1) in the presence or absence (control) of TEA 10^{-3} and 10^{-2} mol litre^{-1}. Propofol-induced relaxation was reduced by TEA. The Wilcoxon signed rank test was used (*P<0.05). Values are mean (SEM), n=6–7.

The dependency of a functional endothelium for the action of propofol has been investigated in several species and vascular beds. Our results indicate that propofol relaxes human omental arteries and veins in an endothelium-independent manner. This also occurs in the rat aorta,[21 23 25] canine coronary artery,[22] pig coronary artery[24] and rat pulmonary artery.[25] Propofol has also been found to have endothelium-dependent effects. In the bovine coronary artery, propofol is more potent in endothelium-intact vessel segments than in endothelium-denuded vessel segments.[18] In rat coronary artery, the relaxant effect of propofol is endothelium-dependent.[20] The view that propofol acts differently depending on the species or vascular region is supported by other workers.

L-NAME and indomethacin did not affect the responses to propofol. This indicates that neither nitric oxide formation nor prostanoid synthesis is involved in propofol-induced relaxation in human omental arteries and veins. In contrast, in the rat coronary artery, nitric oxide and prostanoids are important for propofol-induced relaxation,[20] and in rat aorta and pulmonary artery, prostanoid synthesis is reported to be involved in propofol-induced relaxation.[25] Our results indicate that propofol may not interact with endothelial mechanisms at basal conditions *in vitro*. However, in the *in vivo* situation, there could be a varying degree of stimulation of the endothelium, for example by substance P and bradykinin, to produce nitric oxide, prostanoids or endothelium-derived hyperpolarizing factor (EDHF) that could affect smooth muscle cells. Any potential effect of propofol on these mechanisms remains to be elucidated.

The relaxant effect of propofol in human omental arteries and veins was reduced by increased extracellular K^+ concentration. Membrane hyperpolarization results from changes in ion conductance. By increasing the extracellular K^+ concentration, the K^+ gradient over the smooth muscle cell membrane becomes smaller, and thus hyperpolarization is inhibited.[13] The effect of KCl implies that hyperpolarization may be involved in propofol-induced relaxation of human omental arteries and veins. Indeed, a similar reduction in the responses to propofol when extracellular K^+ was increased have also been found in the pig coronary artery, where propofol caused less relaxation in vessel segments precontracted with KCl than with norepinephrine, 5-hydroxytryptamine or carbachol.[24] Moreover, in human omental arteries and veins, propofol is less potent in inhibiting KCl-induced contractions than contractions induced by U46619.[28] The reverse of these findings seems to be true for the rat thoracic aorta, where propofol produced greater relaxation in vessel segments precontracted with KCl than with phenylephrine.[21] The evidence for propofol-induced hyperpolarization in our study is indirect. Electrophysiological measurements of actual membrane potential are needed to verify the findings.

Hyperpolarization can be achieved by activating K^+ channels, resulting in K^+ efflux and reduction of smooth muscle tone.[36] To investigate if K^+ channels are involved in propofol-induced relaxation, the effect of three inhibitors of K^+ channels (TEA, glibenclamide and 4-AP) was investigated. Glibenclamide and 4-AP did not affect the responses to propofol, indicating that neither K_{ATP} nor K_V is activated by propofol. In contrast, TEA inhibited propofol-induced relaxation. The effect of TEA indicates that propofol in human omental arteries and veins may activate BK_{Ca}, which results in hyperpolarization and relaxation. In canine coronary arteries, TEA at these concentrations did not affect the response to propofol,[22] again confirming the complex and variable actions of propofol.

The TEA concentration required for inhibition of propofol-induced relaxation was high and selectivity for BK_{Ca} might be questioned. In addition, TEA has been proposed to have muscarinic antagonist properties.[37] In our study, the muscarinic antagonist atropine had no effect on propofol-induced relaxation, indicating that relaxation was not mediated via muscarinic receptors. This also implies that the effect of TEA on propofol-induced relaxation is unlikely to be non-specific inhibition of muscarinic receptors.

Clotrimazole, an inhibitor of the cytochrome P450 system, has been shown previously to inhibit nitric oxide–prostanoid-independent relaxation.[38] Clotrimazole is also an inhibitor of the intermediate conductance Ca^{2+}-activated K^+ channel (I_{KCa}).[39] In our study, clotrimazole had no effect on propofol-induced relaxation, indicating that propofol may not relax human omental arteries and veins via a cytochrome P450-derived product, and it does not activate I_{KCa}.

In summary, the relaxant effect of propofol on human omental arteries and veins was endothelium-independent and probably involved hyperpolarization, possibly resulting from activation of BK_{Ca}.

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Effects of normobaric oxygen on ciliary beat frequency of human respiratory epithelium

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Summary

Respiratory infection is a major cause of morbidity after general anaesthesia. Impairment of respiratory ciliary beat frequency (CBF) by different stress factors causes a decrease in mucus transport rate (MTR). We have tested the effect of different concentrations of oxygen on CBF of human respiratory epithelium in a prospective, randomized, *in vitro* study. Samples of superficial mucosa of the inferior nasal turbinates of 20 non-smoking healthy volunteers were harvested and exposed to three different oxygen environments (group I=21% oxygen, group II=60% oxygen and group III=95% oxygen) for 2 h. In 50% of the samples, exposure time was prolonged. At 30, 60, 90, 120 and 240 min, light microscopic images of cilia activity were videotaped and CBF was later assessed in slow motion. Compared with baseline, group I showed no difference in CBF throughout the study. CBF was increased in group II from mean 9.7 (SD 0.4) to 11.2 (0.4) Hz (16%, P<0.001) and in group III from 9.5 (0.6) to 12.1 (0.5) Hz (28%, P<0.001) at 120 min. After 240 min of exposure to 95% oxygen, the CBF trend in group III was reduced to 11.8 (0.6) Hz but still remained above baseline. We conclude that oxygen appeared to have a dose- and time-dependent accelerating effect on CBF. Prolonged exposure to high oxygen concentrations reversed this trend. Direct oxygen toxicity ("oxygen stress") is a possible explanation for this effect. These changes may result in impaired MTR. (*Br. J. Anaesth.* 1998; **80**: 660–664)

Keywords: lung, trachea; lung, mucus; oxygen, toxicity

Respiratory infection is a major cause of morbidity after general anaesthesia. Impairment of respiratory ciliary function produces a decreased mucus transport rate, leading to mucus retention and atelectasis. Subsequently, pneumonia may occur in these patients. An efficient mucociliary transport system depends on adequate ciliary function (ciliary beat frequency (CBF), structure, coordination), and on the volume and physical properties of mucus. The depressant effects of different volatile anaesthetics on human respiratory CBF has recently been reported.[1] However, the early effects of normobaric oxygen on ciliary function have not been evaluated. Therefore, we investigated the effect of different oxygen concentrations after short exposure times (up to 4 h) on CBF using an *in vitro* model.

Subjects and methods

After obtaining approval from the Ethics Committee (Landesärztekammer) and informed subject consent, we studied 20 non-smoking volunteers. None had acute or chronic diseases of the upper respiratory tract or were receiving any medication that would affect the respiratory system. On three different occasions, they were scheduled for tissue sampling at the same time of day. Fresh samples of superficial mucosa of the inferior nasal turbinates were obtained using a fine curette. Samples were transferred immediately onto slides and wetted with nutrient medium (RPMI 1640 (10×Lsg.), Dulbeccos, Eggenstein, Germany). To evaluate viability (visible ciliary beating), each sample was viewed in a hanging drop using a high resolution interference contrast microscope (Leitz, Orthoplan ICTL, Leitz, Wetzlar, Germany). The microscope table was heated to 37°C. A conventional air-conditioning system maintained the surrounding room air (21% oxygen) at 65–75% humidity. Viable tissue was loaded onto a polycarbonated membrane (Transwell-clear, 3.0 μm pore, TC treated, Costar Corporation, Cambridge, MA, USA). The tissue carrying membrane was mounted into a special exposure chamber, so that the base just dipped into the nutrient medium. We used a specially designed chamber (HWS 2×4,5l; H W Schmidt-Labortechnik, Mainz, Germany) to expose the tissue to various atmospheric environments (fig.1). The volume of the chamber was 4.5 litre. Inside temperature and humidity were controlled by warm water at 37°C and 99% relative humidity, respectively (testoterm-601, Testo GmbH, Lenzkirch, Germany). The nutrient solution was buffered to pH 7.4 using 5% carbon dioxide added to the various atmospheric environments and repeat measurements were performed to monitor actual pH (pH-Meter 761 Calimatic, Knick, Elektrische Messgeräte, Berlin, Germany) and osmolarity (Advanced Microosmometer, Model 3M0 Plus, Advanced Instruments, MA, USA). Air and 5% carbon dioxide, and then various oxygen–carbon dioxide mixtures were passed through the chamber at a flow rate of 1.5 litre min^{-1} controlled by a flowmeter (Rotameter,

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†This article is in memory of P. P. Kleemann, who is deceased.

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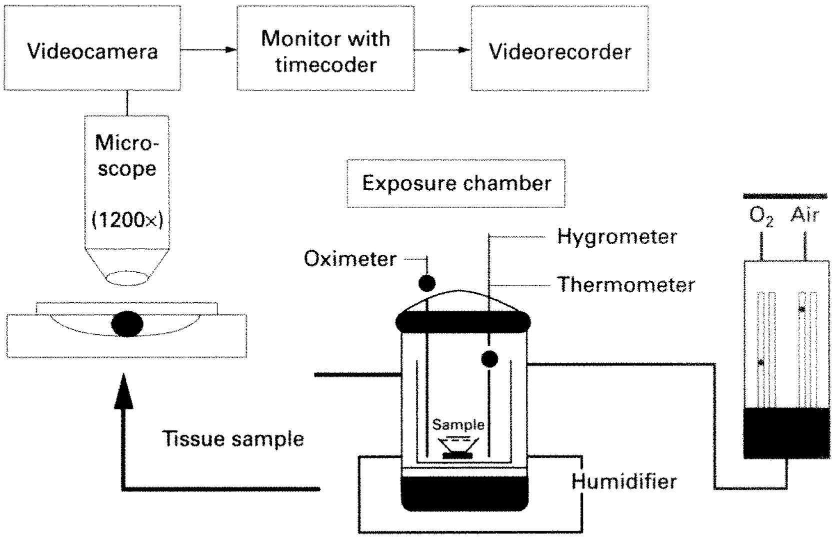

Figure 1 Experimental set-up (see methods for further details).

Drägerwerke, Lübeck, Germany). The oxygen concentration within the chamber was monitored by an oxygen sensor (Datex Capnomac II, Hoyer-Bremen, Germany). Thus the cells were wetted and supplied with nutrients by capillary forces through the pores of the membrane while the surface was exposed to a variety of oxygen concentrations.

Tissue was dissected into small pieces using a micropipette and moistened with RPMI 1640. After a primary stabilization period of 1 h in the exposure chamber (21% oxygen), samples were loaded onto coverslips, which were then placed upside down on a welled microscope slide. Using the same interference contrast microscope at high resolution (oil immersion at ×1200), the activity of the ciliated cells was viewed and a baseline recording obtained. The image from the microscope was transmitted to a high resolution video system (Videorecorder, Panasonic AG-6720, Matsushita Deutschland, Germany; Videocamera, Sony AVC-D1, Sony Deutschland, Köln, Germany) and recorded onto videotape. Tissue samples were then exposed to different oxygen concentrations over a period of 120 min. At 30, 60, 90 and 120 min of exposure, cilia activity was videotaped. For 50% of the cohort, exposure time was prolonged to 240 min (fig. 2). Cilia activity in this subset was recorded after 180 and 240 min of exposure. At each time, 10 different areas of the sample were viewed and subsequently recorded for 10 s each.

To determine CBF, video-recordings were later viewed in slow motion and CBF of each sample and area were counted manually and averaged by an investigator blinded to the oxygen concentration. Subsequently, percentage change from baseline CBF was calculated at each time for each tissue.

The harvested cells of each individual were allocated randomly to one of three groups, thus ensuring that respiratory epithelial cells of each volunteer were exposed to all three gaseous environments. Tissue in group I (n=20) was exposed to a mixture of 21% oxygen and 5% carbon dioxide during the entire study and served as controls. The experimental groups received higher concentrations of normobaric oxygen: group II samples (n=20) were exposed to a room air–oxygen–carbon dioxide mixture (60% oxygen and 5% carbon dioxide) and group III samples (n=20) to a oxygen–carbon dioxide mixture (95% oxygen and 5% carbon dioxide), respectively.

STATISTICAL ANALYSIS

Statistical analysis was performed using Wilcoxon matched pair signed rank tests, assuming unequal differences. Significance was taken at $P<0.05$.

Results

No complications were noted while harvesting the tissues from the inferior nasal floor of the volunteers. Greater than 95% of the samples contained enough viable cells and were used in the study. Using

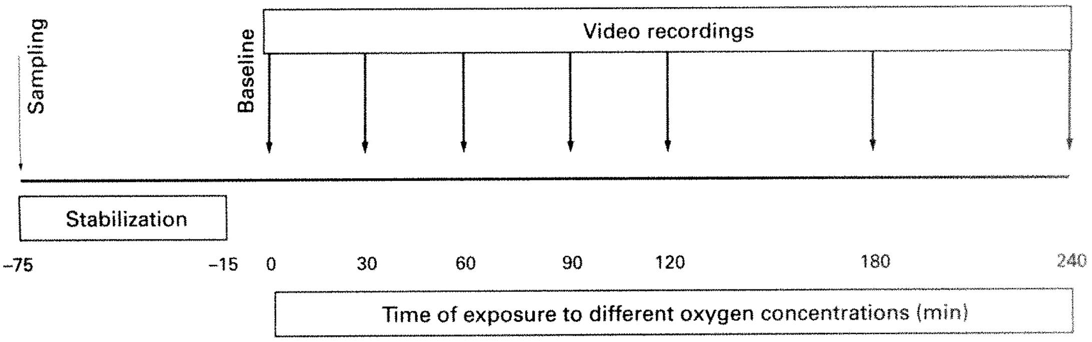

Figure 2 Summary of the experimental procedure. After a primary stabilization period of 1 h, the activity of ciliated cells was viewed and a baseline recording obtained. Tissue samples were exposed to different oxygen concentrations over a period of 120 min. At 30, 60, 90 and 120 min of exposure, cilia activity was videotaped. For 50% of the cohort, exposure time was prolonged to 240 min.

Table 1 Ciliary beat frequency (CBF) of respiratory epithelial cells at different times in the three gaseous environments. All tissue samples were observed for 120 min (n=60). Half of the cohort was exposed for up to 240 min (n=30). Data are mean (SD) and percentage change from baseline

	21% Oxygen		60% Oxygen		95% Oxygen	
Time (min)	CBF (Hz) (n=20)	% Baseline (n=20)	CBF (Hz) (n=20)	% Baseline (n=20)	CBF (Hz) (n=20)	% Baseline (n=20)
0	10.2 (0.9)	0.0	9.7 (0.4)	0.0	9.5 (0.6)	0.0
30	10.3 (0.9)	0.7	10.2 (0.4)	5.4	10.9 (0.8)	15.1
60	10.3 (1.0)	0.6	10.7 (0.4)	10.8	11.6 (0.5)	22.6
90	10.3 (0.8)	0.3	11.0 (0.3)	13.2	11.8 (0.6)	25.0
120	10.3 (0.8)	0.9	11.2 (0.4)	16.0	12.1 (0.5)	28.5
	(n=10)	(n=10)	(n=10)	(n=10)	(n=10)	(n=10)
180	10.4 (0.9)	0.7	11.3 (0.4)	16.7	11.9 (0.7)	24.2
240	10.4 (1.0)	0.3	11.3 (0.3)	17.0	11.8 (0.6)	22.6

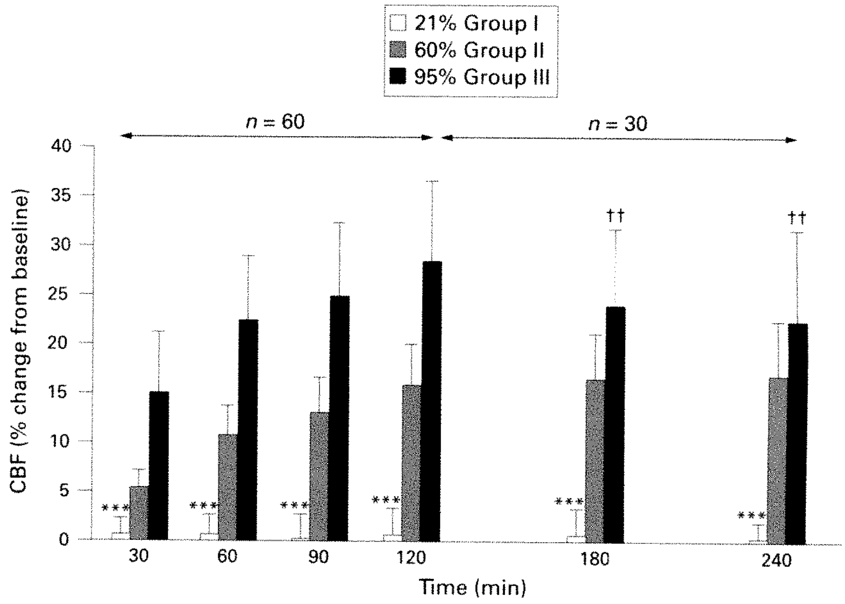

Figure 3 Ciliary beat frequency (CBF), expressed as percentage change from baseline, in different gaseous environments (21%, 60% and 95% oxygen). ***$P<0.001$ compared with groups II and III; ††$P<0.01$ compared with 120 min exposure to 95% oxygen (group III). (See results for more details.)

interference phase microscopy, we measured CBF in a total of 3600 cells. Under room air conditions, baseline mean CBF was mean 10.2 (SD 0.9) Hz (group I) (table 1). Group I served as the control and showed no difference in CBF throughout the study. After 240 min of exposure to room air, mean CBF was similar to that of baseline (10.4 (1.0) Hz). In contrast, exposure to increased concentrations of oxygen increased CBF in a dose- and time-dependent manner (table 1). The increase in CBF compared with controls (group I) appeared more rapid with the higher (95%) than with the intermediate (60%) oxygen concentration (fig. 3).

In group II, baseline mean CBF (9.7 (0.4) Hz) increased by approximately 5% to 10.2 (0.4) Hz after 30 min of exposure to 60% oxygen ($P<0.002$). With 95% oxygen (group III), the increase in CBF was greater, reaching maximum values of 9.5 (0.6) to 12.1 (0.5) Hz after 2 h of exposure (28% increase, $P<0.001$). When exposed for 4 h, the activity decreased to 11.8 (0.6) Hz (6% decrease from the maximum value at 2 h, $P<0.002$) (table 1).

Discussion

A large number of patients are dependent on continuous high inspiratory oxygen concentrations because of pulmonary disease. Many breathe spontaneously, while others require ventilation using various apparatus in intensive care units or operating rooms. However, the long-term influence of high normobaric oxygen on ciliary function of human respiratory epithelium has never been investigated. It is difficult to extrapolate results from animal studies on different species to human ciliary beat function[2 3] and viable epithelial cells from humans are available only through invasive procedures such as bronchoscopy. However, Rutland and colleagues[4] and Roth and colleagues[5] described similar ciliary beat patterns of tracheal and nasal epithelia; thus, we decided to use nasal tissue samples from healthy subjects. The influence of different agents on respiratory epithelium has been studied by calculating CBF after exposure.[6 7] Human respiratory epithelium is highly sensitive to dehydration, and changes in pH[8 9] and temperature[10]; thus an aqueous milieu was mandatory. We used a specially designed exposure chamber, established recently by Riechelmann and colleagues,[11] to provide constant temperature, humidity, air flow and oxygen concentrations. The nutritive solution was maintained at 37.0° C and pH at 7.5 and in controls (21% oxygen) there was no change in ciliary activity throughout the study. CBF was measured using the transmitted light technique combined with a high speed video-microscope.[7] In pilot experiments, this method was found to correlate well with the correlation analysis laser light scattering system (CALLS) technique.[12] We found basal ciliary beating of all harvested cells at a frequency of 10.2 (0.9) Hz. This was similar to the report of Jackson and colleagues,[13] while Dulfano and colleagues[14] reported basal CBF of respiratory epithelium at 12.8 Hz.

After exposing tissue samples for 2 h to different hyperoxic gas mixtures, we found a dose- and time-dependent increase in CBF of up to 28% with 95% oxygen compared with baseline. However, prolonged exposure (4 h) caused a 6% decrease in CBF compared with the high activity state after 2 h of exposure.

These two important findings need to be discussed further in the context of the recent literature. First, the observed continuous increase in CBF within the first 2 h of exposure to high oxygen concentrations was similar to that of Harrison, Wong and Yeates[15] in a canine model. Other groups found a significant increase in CBF after exposure to different mediators related to inflammation.[16] Bonin, Phillips and McCaffrey[17] and Khan, Dolata and Lindberg[18] found that inflammatory substances (PGE_2, prostacyclins) can upregulate CBF in respiratory cells. Substance P seems to have similar effects.[19] Rapid increases in CBF were also induced by "free radicals".[20] Thus our findings suggest a direct effect of oxygen on human respiratory cells.

Prolonged oxygen exposure may trigger a cascade of inflammatory mediators (PGE_2, prostacyclins, substance P)[21] subsequently leading to inflammation of the respiratory mucosa[22] and altered clearing of mucus. However, some toxic agents can cause an immediate reduction in CBF, even after brief exposure.[23–25] Kukreja and colleagues[26] reported inactivation of Ca^{2+}–ATPase under H_2O_2 resulting in reduced cellular concentrations of ATP. Yoshitsugu and colleagues[20] induced a decrease in CBF after application of HO^- for 5 min. These findings may be explained by a direct toxic effect of these substances on the epithelium, immediately impairing ciliary function. Additionally, they may relate ciliary activity to the energy status of respiratory cells.

The second important finding of our study was a delayed decrease (6%) in CBF after prolonged exposure (4 h), again confirming the findings of others. Boat[27] investigated CBF of tracheal epithelium of newborns under different oxygen concentrations. He found ciliary stasis at 48–96 h after exposure to 80% oxygen. The observed reversal of the early increase in CBF may represent progressive energy failure or direct oxygen toxicity at a cellular level after prolonged exposure to high oxygen concentrations. However, further studies are needed to clarify the exact mechanisms. Study design should allow tissue to recover from oxidative stress or provide additional ATP during prolonged exposure. Also, the exact time course of the decrease in CBF needs to be investigated over extended periods (i.e. 48–96 h). Further research in this area is important and clinically relevant, as prolonged exposure to normobaric hyperoxia reduces the mucociliary transport rate. Sackner and colleagues[22] observed a 40% decrease in mucociliary transport rate after 2 h in dogs breathing a hyperoxic gaseous mixture. Additionally, the role of discoordination of ciliary beat as a result of cellular damage needs to be addressed. In inflamed respiratory epithelium, reduced mucociliary transport rate is a result primarily of discoordination with reduced CBF being less important.[28]

In summary, our data suggest that oxygen had a dose- and time-dependent accelerating effect on CBF of human respiratory cells up to 2 h after exposure. In the context of recently published work, this may be explained by "oxygen stress" to the respiratory epithelium at a cellular level. In addition, we were able to show that during prolonged exposure (>2 h), high oxygen concentrations (95%) reduced CBF. Both an increase and late reduction in high CBF represent patterns of impaired physiology of human respiratory ciliary cells and may indicate impaired mucociliary transport capacity of these cells. From a clinical prospective, we conclude that prolonged exposure to high oxygen concentrations appears to indicate increased risk of respiratory infection and therefore should be avoided whenever possible.

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REVIEW ARTICLE

Computed tomography and pulmonary measurements

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Computed tomography (CT) was first developed to measure accurately radiographic density, rather than as a method of imaging.[19] Although subsequent development concentrated on the imaging potential of the method, some recent studies have used the ability of the method to quantify radiographic density, to provide precise measurements of lung regions and infer differences in regional properties.

CT measures the radiographic density of an array of small discrete parts of the body. Usually, each of these parts in a single tomographic slice is represented as a pixel, and these pixels are displayed as the units of a two-dimensional image. The operator allocates a range of grey shades between black and white (tone range) to a particular range of radiographic densities, so that the densities of interest lie between black and white in the visual image. For example, when the details of lung tissue are of interest in the image, the density window (measured in Hounsfield units, HU) often chosen is from −500 (black) to −200 (white). These settings can be expressed in terms of the window centre and width. Lung tissue, containing a large proportion of air, has a range of radiographic densities much less than other body tissues, for example the soft tissues of the mediastinum. Consequently, details of lung structure can be shown more clearly by expressing this narrow range of low densities over the whole visual range from black to white. The grey scale that shows how the black and white visual image is related to radiographic density is displayed at the edge of most CT images, and can be altered by the operator to enhance the features of interest.

Each CT image therefore consists of an array of small squares, each with a discrete grey value, that represents the mean radiographic density of a cylinder of tissue, or voxel. The end is represented in position and area by the pixel, and the length is the thickness of the CT slice. Although the visual image is often altered to improve the contrast of specific features, the original radiographic density values can be used to obtain more specific information about the properties of the materials studied.

Radiographic density is the property of materials to absorb electromagnetic radiation. This radiation is exponentially reduced on passage through materials, so that the intensity (I) after passing a distance (x) through a material can be expressed:

$$I=I_0 e^{-\mu x}$$

where I_0=radiation intensity incident on the material and μ=linear attenuation coefficient for the material.

Attenuation of electromagnetic radiation is mainly by two processes, photoelectric absorption and Compton scattering. Consequently, factors that influence attenuation include the physical density of the material, and the atomic number, electron density and mass electron density of the materials. With an energy spectrum of 120–140 keV, which is the energy used for medical radiology, attenuation is mainly by Compton scattering, which depends on the electron density of the material. As the relationship between electron density and physical density is relatively constant for most materials, there is a good relationship between attenuation and electron density and a reasonable relationship with physical density. A series of exact shapes made from different woods have a linear relationship between physical and radiographic density, in the range 0.37–0.9 g cm^{-3}, but the relationship is non-linear at greater densities.[34] However, water, which is an important body constituent, does not follow exactly the same relationship as other materials.[34 44]

Absorption of radiation which has lower energy is by photoelectric absorption, and this depends more on the atomic number of the material. Consequently, physical density and radiographic density may be variably related according to the range of electron energies from the source, because the absorption of radiation with different energies varies with the material studied.[37] This is made more complex by the more marked attenuation of the lower energies (beam hardening). Variations in operating energy can cause significant error in measurements,[56] and change in position of the subject in the x-ray beam can also affect the results.[26] Another potential source of error is variation in detector gain, which is more likely with measurements of low attenuation materials such as the lung.[56] Density assessments between different scanners may differ significantly.[26] However, despite these sources of variation, repeat measurements in optimal conditions can be highly reproducible.[56]

Partial volume effects

When CT is used to measure lung density, dense tissues adjacent to the lung can influence the average slice density. This is because of the limited spatial

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Keywords. measurement techniques, computed tomography; ventilation, regional; lung, volume

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resolution of the system, so that a single voxel may contain both lung tissue and also some adjacent dense tissue in the slice. This is the partial volume effect. This effect becomes greater when the overall area of the lung slice is small. However, the effect is predictable and a correction can be applied. Such slices are obviously present at the lung apex, but there are also small areas in the crescentic slices posterior to the diaphragm at the lung base.[4] Pulsation of blood vessels, over the time necessary for a scan, is another factor that increases the density of a voxel.

Radiographic density is most often expressed in Hounsfield units, a dimensionless index of attenuation that is related to the attenuation of air and water. The attenuation coefficient of air is allocated a value of −1000, and water is allocated an attenuation coefficient of zero.

The attenuation value, $CT_m=1000.\ (\mu_m-\mu_w)/(\mu_w-\mu_a)$ where μ_w, μ_a and μ_m=attenuation values for water, air and the tissue being measured, respectively. If a linear relationship is assumed between Hounsfield number and density, then radiographic density values from CT provide a non-invasive and anatomically localized index of tissue density. In the lung, the relative content of air and solid material (either tissue, or blood and other fluid such as oedema) can be calculated with reasonable confidence. The volume of solid organs can be measured to within 5% using CT.[1] Determination of the boundaries between lung and chest wall can be difficult, particularly if collapsed lung tissue is present.[20] Studies have used threshold values of −200 HU to distinguish lung from soft tissue, although in some disease states lung tissue may have densities greater than this. Operator-controlled measurement of lung density can vary by up to 15 HU for regional measurements, and poor patient co-operation has a large effect. Semi-automatic methods can improve reproducibility although density estimates are greater because of partial volume effects.[20]

Regional changes in radiographic density of the lung in association with abnormalities of regional ventilation have been described since the 1930s, and changes in direct x-ray density during the breathing cycle were related to local pathology in the 1960s.[23] Although CT studies of changes in lung tissue during respiration are limited, because of the radiation burden, there are reports of changes in lung properties with changes in lung volume in normal subjects,[45] in patients during anaesthesia[14]and in intensive care.[5]

REGIONAL DIFFERENCES

How can the regional differences in radiographic density be related to lung expansion, and changes in radiographic density related to regional ventilation? First, we must establish a logical way to express regional ventilation. When a whole excised lung is inflated, expansion is relatively uniform. In an excised lung, therefore, lung volume could be expressed in terms of a proportion of the volume of the lung at any value convenient position on its pressure–volume characteristic. The most logical volume to use is total lung capacity (TLC). The degree of expansion of the lung is expressed as a fraction of the volume it would occupy at TLC. This approach is necessary because *in vivo*, the lung is often not uniformly expanded. This method takes into account regional variations in expansion, by expressing the volume of a lung region as a proportion of the volume it can potentially occupy.[32] As lung tissue is almost uniformly distended at TLC, even within the thorax, this allows an expression of ventilation as if it were "per alveolus". Although this approach allows expression of the relative expansion of the lung regions, it requires knowledge of the volume of that region at TLC. When regional expansion is measured by the now classical technique of the inhaled radioactive isotope ^{133}Xe, using external scintillation counters, this knowledge can be obtained from the counts taken during a breath-hold at TLC, with a uniform lung gas tracer concentration. In this way, having measured regional lung volume, regional differences in ventilation can be subsequently expressed in terms of "ventilation per maximal lung volume for that region".[31]

Clearly, if different denominators were to be used to express the expansion of different lung regions, we would obtain illogical results. For example, consider a poorly expanded lung region that is at 10% of its maximal volume and is then expanded to 20% of its maximal volume. If we were to express its expansion in terms of its starting volume, then it would appear to have been expanded by 100%, whereas it has expanded by only 10% of its potential total volume. Therefore, if we are to use radiographic density changes to assess regional expansion and ventilation, we should not consider changes in density in terms of starting density, but rather in terms of the density of the region of interest at full lung expansion.

Denison, Morgan and Millar measured the density of the lung at full expansion.[5] They compared CT measurements of the lung with measurements of a foam-like model surrounded in a body-like shell to simulate the effects of beam hardening. They used bread with a range of consistencies—from moist pumpernickel to dry baguette—to simulate lung densities in conditions from fibrosis to emphysema. They were able to estimate density of the model substances accurately with CT and also measure precisely a volume of water injected into the bread. Normal lungs in supine subjects had a tissue volume of approximately 0.12 ml per ml of total volume at total lung capacity. They noted that in supine subjects, their measurements of density increased at both the apex and base of the lung, and suggested that this was the result of partial volume effects which makes measurements in these lung regions unreliable. On the basis of their estimates of density we can predict the relationship between lung expansion, expressed as a fraction of total lung capacity, physical density in g ml^{-1}, and radiographic density in HU.

At total lung capacity (TLC), lung density D_{TLC}=lung tissue mass/TLC. At any smaller lung volume (*V*L), lung density D_{VL}=lung tissue mass/*V*L. If the lung tissue mass is not affected by the change in volume, then fractional lung expansion *V*L/TLC=D_{TLC}/D_{VL}. (This may not always be a valid assumption as some of the tissue mass consists of blood volume which may alter with expansion.)

From the previous definition of the Hounsfield unit, radiographic density (Hounsfield units)=

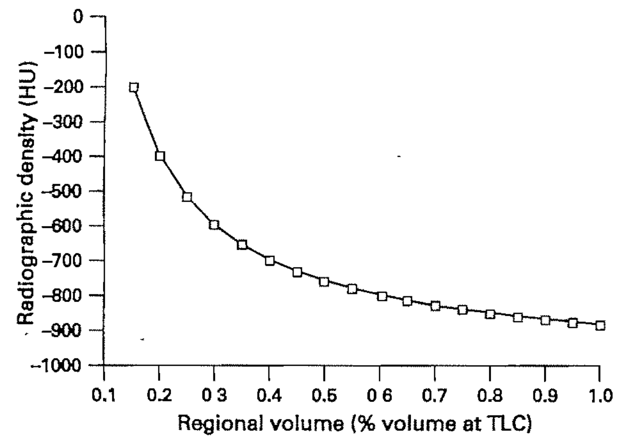

Figure 1 Relationship between regional volume and radiographic density, for a lung density of 0.12 g cm^{-3} at total lung capacity (TLC).

(D_{rL}×1000)−1000. This relationship for the lung is shown in figure 1.

The practical consequences of this reciprocal relationship are illustrated by the example in figure 2.

Lung tissue at FRC is not homogeneously distended. The less well expanded lung has a greater density, as the same mass of tissue occupies a smaller volume. If during an inspiration, ventilation distribution throughout the lung is uniform (in proportion to the volume at TLC) then the less well expanded regions will have a greater change in radiological density.

What components of the lung contribute to radiological density? In normal lungs, these are alveolar gas, lung tissue and blood in the capillaries. Increasing distension of the lung during inspiration leads to a progressive reduction in radiological density of the entire lung.[4 45 46 55] There is a vertical gradient in lung density which can be related, at least in part, to the gradient in regional expansion. This gradient becomes less as lung volume increases towards TLC.[45 46 55 57] The distribution of density values in the entire lung, which is unimodal during maximal inspiration, becomes bimodal during expiration, an effect which is seen only in the dependent parts of the lung.[46 55] In animal studies, CT density was relatively constant for any particular vertical height, but CT measurements of lung gas volume systematically underestimated gas volume measured by helium dilution.[54] Some of this systematic error is caused by partial volume effects. In lung disease such as emphysema where the relative volume of gas is increased[50] or fibrosis where the tissue volume is greater,[13] changes in CT density can be related to clinical, physiological, and pathological features.

In abnormal lungs, there may also be a considerable amount of extravascular water in the form of oedema, either interstitial or in the airspaces. For example, haemodialysis can reduce overall lung density, both in aerated regions with densities of −350 HU, and also in less well aerated regions with densities of −50 HU.[55] When experimental pulmonary oedema is caused by increasing left atrial pressure, lung density increases by approximately 70%. The increase is more pronounced in central and dependent lung regions.[18] In patients with chronic heart disease, where pulmonary vascular hypertrophy is likely, lung density measurements with CT can be related to the degree of pulmonary hypertension.[53] In addition, it is clear from early x-ray density studies that the fluctuations in pulmonary artery pressure and x-ray density are closely related, indicating that changes in the volume of pulmonary vascular structures within the lung tissue have an important effect on radiological density.[25]

A valuable study used positron tomography to provide separate estimates of the tissue and blood components in supine subjects, breathing at normal tidal volumes. Measurements were made over a 15-min

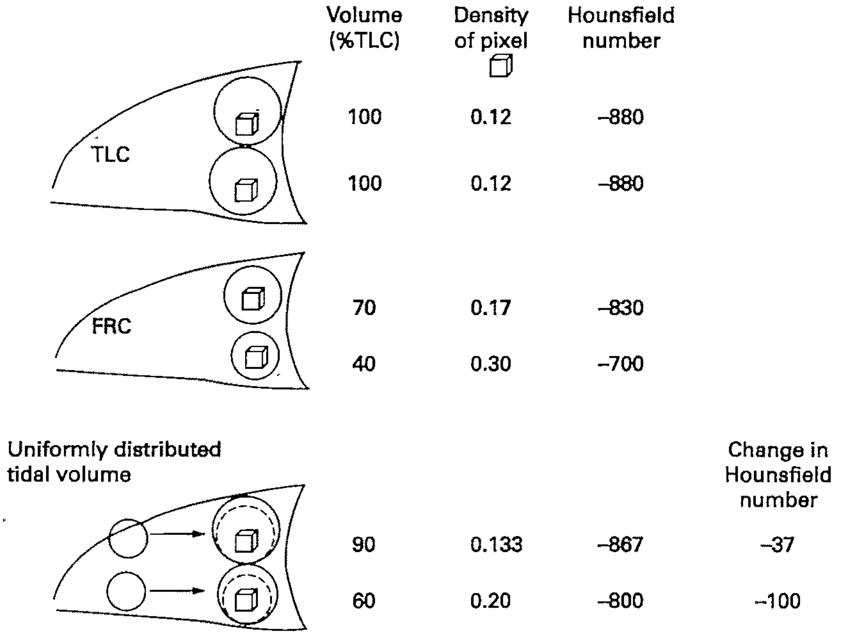

Figure 2 Illustration of changes in density with uniform regional ventilation. At functional residual capacity (FRC), lung tissue is less expanded in dependent regions (at 40% of the volume at total lung capacity (TLC)) than in the upper regions (70% of TLC volume). These regions still consist of the same mass of tissue that they had at TLC, but they now fill less volume: for example, the density of the lower region is now 100/40 greater than at TLC. If the lung then expands uniformly by 20% of TLC volume, the relative change in density is far greater in the dependent region.

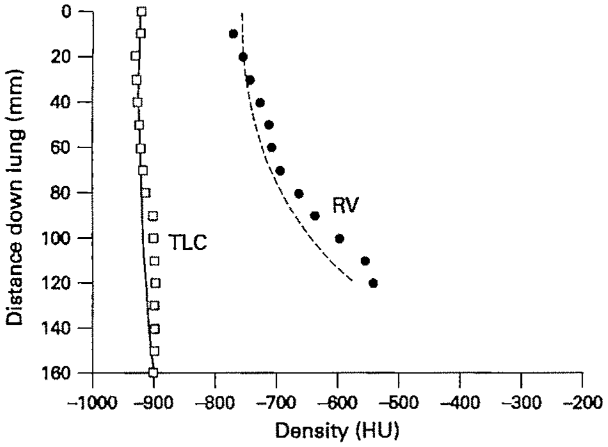

Figure 3 Predicted (lines) and observed (symbols) values for lung density, at total lung capacity (TLC) and residual volume (RV). Data are re-plotted from Millar and Denison.[33] Note the deviation of the observed densities, indicating that density is affected by an additional gradient, probably vascular tissue volume.

period. This method did not have very good spatial resolution (1.6 cm) and therefore partial volume effects from overlapping of different tissues were great. Nevertheless, by using both transmission tomography with a source of ^{68}Ge, and emission tomography after labelling blood with ^{11}C carbon monoxide, the separate contributions of lung tissue density and blood density were separated in five volunteers. An anteroposterior gradient of lung density was found from approximately 0.2 g cm^{-3} in the uppermost to approximately 0.4 g cm^{-3} in the lowermost region. Mean lung density was 0.29 g cm^{-3}. Most of this gravitational gradient in density was attributable to blood and only a small amount to extravascular structures, considered to mostly represent lung tissue.[44] Such observations are consistent with direct measurements of capillary blood and tissue expansion in animal studies[8 9] and are supported by CT studies in dogs,[34] and observations by CT studies in humans. Such studies show a gradient in lung density from ventral to dorsal regions, which is reduced but not abolished on inspiration.[33 45] The gradient in density is reduced as transpulmonary pressure increases, but is still prominent at a transpulmonary pressure of 15 cm H_2O and is not affected by voluntary inspiration that increases transpulmonary pressure to 20 cm H_2O.[57]

Such findings should be compared with measurements of the gradient of alveolar volume by radioactive gas tracer methods, which show that the alveoli become progressively more uniformly expanded as overall lung volume increases, and hence the gravitational gradient in alveolar size becomes progressively less with increasing transpulmonary pressure.[31] The discrepancies between the vertical distribution of alveolar volume, uniform at TLC, and the vertical distribution of radiological density, which persists at TLC, show clearly that radiological density does not merely measure "aeration" but a combination of aeration, blood volume and interstitial fluid volume. As blood has a much greater density, small changes in blood volume can affect radiological density far more than expansion or contraction of aerated lung tissue. For example, a Valsalva manoeuvre can decrease lung radiological density, particularly in more dense regions, although lung volume and alveolar expansion are not affected.[46] If we wish to relate accurately changes in lung radiological density to changes in alveolar volume (i.e. to infer changes in regional expansion or regional ventilation) then this is possible only if we know that the blood volume of the region remains unaltered. This may be a reasonable assumption for one gravitational level in the lung. If we compare different levels, then it must be remembered that absolute densities at TLC are different. Millar and Denison[33] conducted an elegant study of the vertical gradient in CT density of the lungs of normal subjects. They found a discrepancy between the theoretical density of the lung, calculated on the basis of a simple hydraulic gradient of pressure in lung tissue, and the actual radiological density of the lung (fig. 3). They suggested that the discrepancy was because blood vessels increased in size in more dependent parts of the lung, imposing a second gradient in the tissue mass that contributes to radiological density. This effect is not relevant when regional volume change is considered on the basis of volume/maximal volume, as the tissue mass plays a negligible role in this estimate.

These considerations indicate that the vertical gradient in CT density is likely to be the result of two factors: distribution of blood volume and distribution of lung expansion. The relative importance of these factors is not clear. How much these factors interact is also unclear, and such interactions may also be affected by mechanical ventilation, changes in circulating lung volume, pulmonary haemodynamics or pulmonary vascular disease.

Lung density changes with position,[7] vertical gradient[36] and positive end-expiratory pressure[5] have been studied in normal subjects and patients with ARDS in a series of studies by Gattinoni and his team, which have been summarized recently.[35] They computed the regional distribution of tidal volume, but expressed this as a fraction of the volume of the lung section measured, not as a fraction of lung volume at TLC.[6] This would not have been possible in patients with severe oedema and other pathological changes in the lung, as the ratio of gas to total weight, when lung tissue is fully distended, is unknown. They found an increase in vertical density gradient in patients with ARDS. Such a density gradient has been reported in alveolar oedema, but not in interstitial oedema.[58] They found that positive end-expiratory pressure allowed dependent lung regions to remain distended and thus the distribution of ventilation became more homogenous. A potential source of error that these workers did not consider is the possibility that when alveolar pressure was increased, blood volume in capillaries could have been reduced, and this could decrease CT density. Such a decrease in density would, on the basis of their analysis, be interpreted as an increase in gas volume, and hence ventilation. For example, they reported that by increasing values of PEEP over a threshold value, there was a decrease in density in some lung slices, particularly the dependent ones. They attributed this to the pressure necessary to open compressed lung units, but a similar change could occur if the pressure were reducing tissue volume. Puybasset and co-workers have also used CT measurements in patients with ARDS to assess the

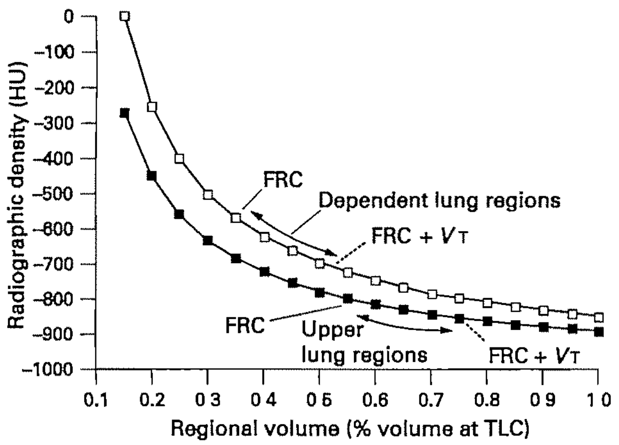

Figure 4 Relationship between radiographic density and regional volume for lung regions in the upper region with a density of 0.11 g cm^{-3} (closed symbols) and dependent regions with a density of 0.15 g cm^{-3} (open symbols), indicating the possible range of volume during spontaneous ventilation from functional residual capacity (FRC) to FRC and tidal volume (FRC+V_T) (data from Reber and colleagues[41]).

distribution of disease,[39] anatomical changes[38] and aeration.[40]

Hedenstierna and co-workers, in a series of studies over many years,[2 10-12 14-17 21 22 27 28 41 42 47 48 50 51] have studied the development of apparent atelectasis ("contrasting densities") in subjects during anaesthesia and after abdominal surgery. Small patches of increased density developed during anaesthesia in dependent lung regions, and would move if the position of the subject changed. These appearances could be prevented or reduced by selective inflation of the dependent lung if the subject was in the lateral position,[22] or by phrenic nerve stimulation in the supine subject.[16] The increased density was related to gas exchange abnormality, particularly shunt, measured by the inert gas infusion method. However, the exact relationship between these areas of increased density and overall gas exchange impairment was not clear. For example, gas exchange efficiency during anaesthesia decreases with age, associated with an increase in lung regions with a small $\dot{V}/\dot{Q}$ ratio, whereas the amount of increased density found on CT in older subjects was no greater than in younger subjects, and there was no relationship between shunt and age. Nevertheless, areas with increased radiological density on CT corresponded to areas of low ventilation/perfusion detected by independent methods of measuring distribution of ventilation and blood flow. In some circumstances, such as ketamine anaesthesia, in which lung volume did not decrease after induction of anaesthesia, such CT changes were not detected.[52] The areas of increased density appeared to be made worse by 100% oxygen: subjects given 100% oxygen for 3 min before induction of anaesthesia had both a greater shunt and more radiological opacity.[42]

Although these workers generally used a visual method to identify areas of atelectasis in a single transverse CT image, usually taken just above the diaphragm, they subsequently showed that this particular region may not be greatly representative of the lung as a whole. For example, in nine anaesthetized supine patients, the mean distribution of blood flow to the most caudal CT slice was less than 10%, in contrast with the 70% for two slices that were placed closer to the carina.[51] Retrospective analysis of their radiological data showed that in awake subjects there was a single population of densities of lung voxels, with a mean density of approximately −790 HU. After induction of anaesthesia, a small separate population of voxel densities was commonly found with densities of −100 to +100, although in some subjects the density of this second population was less, with densities in the range −300 to +50.[29] Previous workers have reported a population of voxels with a greater density, of about this range of values, that became evident in expiration in normal conscious subjects.[46 55]

The 95% confidence limits for estimates of areas of increased density were more than 1%, and mean area was 3.7%, so the precision of the previous method of visual identification is not very great. This poor precision was often not apparent in previous studies where analysis had been made using regression methods only. Furthermore, in none of these studies does the assessment appear to have been performed using observers who were unaware of the state of the patient.

The hypothesis generated by these measurements is that the association between lung volume decreases and the appearance of areas of atelectasis is causal.[2] However, two similar studies do not directly support this causal link. First, CT studies in dogs during pentobarbital anaesthesia showed few and less marked densities.[28] The authors expressed some reservations about these findings and suggested that these increased densities could have been caused by vascular congestion. As blood is probably the most important component of the radiographic density of normal lungs, even small increases in capillary volume increase density considerably. Second, when lung volume was reduced in conscious human subjects, by physical restriction and compression of the chest wall, no regions of increased density were noted. Values for mean radiographic density were not reported in this study, although these would have been of considerable interest.[49]

The same group of investigators reported changes in radiographic density in the entire lung, before and after induction of anaesthesia.[41] Despite the fact that lung volume is usually reduced by anaesthesia, mean lung radiographic density did not alter. They also examined regional changes in lung density and compared awake and anaesthetized patterns, but in their analysis they assumed that gas distribution was proportional to changes in attenuation.

If the changes in density with respiration are to be used to infer regional changes in volume, the regional density at TLC has to be known. Different values are reported, and density changes with the range of the vertical height of the lung because blood content is greater in dependent regions. However, a careful study of lung mechanics and CT changes in supine subjects reported that near TLC, the upper and lower parts of the lung have densities of approximately −890 HU and −850 HU, respectively.[57] Based on the relationship derived above, this gives the relationships between ventilation and radiological density, for upper and lower parts of the lung, shown in figure 4.

Measurements with ^{133}Xe showed that the regional volumes of the upper and lower parts of the lung in a

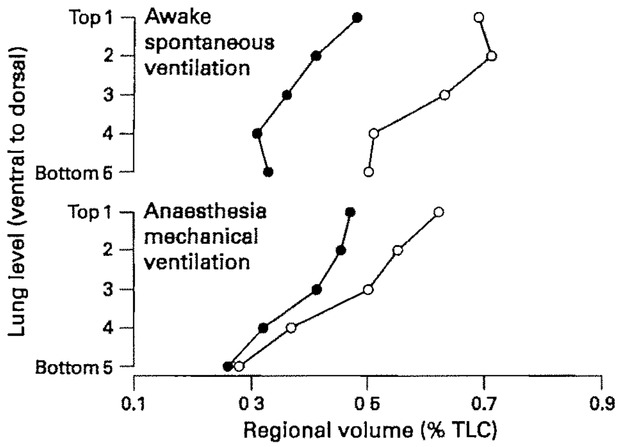

Figure 5 Regional ventilation in the conscious subject (top) and during anaesthesia and mechanical ventilation (bottom) for lung levels from upper (ventral—level 1) to lower (dorsal—level 5). Closed symbols indicate values for expiration and open symbols inspiration. The horizontal distance between the symbols therefore represents regional ventilation. Data calculated from mean values given in Reber and colleagues.[41]

supine subject are approximately 35% and 55% of the volume at TLC[31] and these correspond with the CT density measurements at FRC reported by Reber and colleagues.[41] Figure 4 indicates that at these volumes there are obvious differences in slope of the CT density–regional volume plot, between upper and lower zones. Despite the CT density change being approximately twice as large in the dependent slices, it is clear that the reported changes in CT density represent similar changes in regional volume for the upper and lower parts of the lung.

If we assume a uniform change in lung density from upper to dependent regions, from 0.11 to 0.15, we can infer regional ventilation using the mean radiographic density data provided by Reber and co-workers[41] (fig. 5). The distribution of ventilation is almost uniform in conscious subjects but becomes much more distributed to the upper zones after induction of anaesthesia and mechanical ventilation.

These inferences correspond with measurements of diaphragm images made with a multiple CT method[24] and earlier tracer studies.[43] However, when the volume change for tidal breath during mechanical ventilation is calculated, the value obtained is less than during spontaneous ventilation. This is unlikely, because generally tidal volume is greater during mechanical ventilation. There are several possible explanations. First, the behaviour of this slice may not be the same during spontaneous and mechanical ventilation modes. The ribcage moves more during mechanical ventilation, and regional lung expansion may be altered between the two types of ventilation. More likely, there may be differences in pulmonary capillary blood volume, particularly differences in the shifts of pulmonary capillary blood with respiration, which could explain this discrepancy.

In summary, if appropriate consideration is given to the characteristics of absorption, measurements of radiographic density of the lung allow useful inferences to be made about the distribution of gas, blood and tissue volume. However, comparisons are difficult when more than one component changes simultaneously. The measurements have some inaccuracies, particularly partial volume effects. Finally, radiation exposure limits the use in experimental circumstances, so that studies are limited to those where one or two "snapshots" of lung density can be rewarding.

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British Journal of Anaesthesia 1998; **80**: 672–674

SHORT COMMUNICATIONS

Cricoid pressure: can protective force be sustained?†

T. MEEK, A. VINCENT AND J. E. DUGGAN

Summary

We studied six operating department assistants performing simulated cricoid pressure on a model of the larynx with the arm either flexed to 90° (flexed position) or fully extended with the elbow locked (extended position). Subjects were asked to maintain forces of 20, 30 and 40 Newtons (N) for a target time of 20 min. Subjects rated pain during each assessment on a four-point verbal rating scale (VRS): 1=uncomfortable; 2=hurting; 3=hurting a lot; and 4=agony. Times to onset of pain were short and mean times to VRS 3 at each force studied were: 40 N, flexed position 2.3 min, extended position 5.4 min; 30 N, flexed position 4.0 min, extended position 7.5 min; and 20 N, flexed position 9.6 min, extended position 12.5 min. None of our subjects was able to sustain 40 N for the target time. Mean times to release at 40 N were: flexed position 3.7 min, extended position 7.6 min. Only one subject was able to sustain 30 N and then only using the extended arm. Mean times to release at 30 N were: flexed position 6.4 min, extended position (five subjects) 10.8 min. Two subjects with the arm flexed and five with the arm extended achieved the target time at 20 N. Mean times to release at 20 N were: flexed position (four subjects) 13.2 min, extended position (one subject) 14.6 min. Use of the extended arm consistently prolonged times to pain and fatigue. These findings are relevant to the management of cricoid pressure during failed intubation. (*Br. J. Anaesth.* 1998; **80**: 672–674)

Keywords: intubation, tracheal; larynx, cricoid pressure

Cricoid forces of 44,[1] 40[2] and 30 Newtons (N)[3] have been judged by various criteria to prevent regurgitation. The accepted teaching is that cricoid pressure should be maintained in patients at risk until the airway is secured with a cuffed tracheal tube. However, the ability to sustain effective cricoid pressure has not been studied and we sought to investigate this systematically.

Methods and results

Simulated cricoid pressure was applied to a model of the larynx. The model was made using a 4-cm diameter perspex universal container with a collar of oxygen tubing to form the cricoid cartilage, all covered with Granuflex dressing to simulate skin. A measurement system was constructed to determine applied downward force, based on a load cell (Tedea Hunt Leigh 0–20 kg; accuracy ±0.03% rated load). The applied force was recorded and displayed on a calibrated chart recorder (1 kg=9.81 N).

Six male operating department assistants participated in the study. All were involved routinely in assisting at emergency and obstetric cases and each had more than 5 yr experience in the specialty. They were asked to maintain "cricoid pressure" for a target time of 20 min and to observe the chart recorder throughout to monitor and regulate the force they applied. Each subject was tested at forces of 40, 30 and 20 N in sequence and the interval between tests was at least 24 h. Subjects adopted a natural side-on stance facing towards the "head" and applied pressure using the thumb, index and middle fingers of the dominant hand, as described by Sellick.[4] The "larynx" was placed on a patient trolley at a distance of 25 cm from the subject. The height of the trolley was adjusted in relation to the assistant's stature to obtain comparable mechanical advantage between subjects.

The arm was studied in two positions encompassing the range of arm positions used clinically. In the first set of tests, the "cricoid" was positioned at the height of the subject's elbow, so that the elbow and the wrist were flexed to 90° (flexed position). The tests were repeated with the model at a lower height so that the arm was fully extended with the elbow joint locked and the wrist in the neutral position (extended position). Subjects assessed pain on a four-point verbal rating scale (VRS): 1=discomfort; 2=hurting; 3=hurting a lot; and 4=agony. Times to pain and release were recorded.

Mean times to onset of pain and fatigue-induced release are shown in table 1. Times to pain were notably short. Pain was recorded at VRS 3 in all but one test (20 N force with arm extended). Pain invariably progressed to agony (VRS 4) at 40 N and in all but one test at 30 N where the subject was being tested with the arm extended. At 20 N, five subjects with the arm flexed and one subject with the arm extended reported the pain as agony. The use of the extended arm consistently prolonged times to each pain category.

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Table 1 Times (min) to pain assessments (VRS 1–4) and fatigue-induced release (exhaustion) (mean (SD) [range]). Subjects not reaching a VRS assessment before the target time are not included in means and ranges. †Five subjects, ‡four subjects

	Arm flexed			Arm extended		
	40 N	30 N	20 N	40 N	30 N	20 N
VRS 1	1.1 (0.3)	1.6 (0.4)	2.6 (1.1)	2.0 (0.7)	2.9 (0.7)	5.8 (2.8)
"Discomfort"	[0.8–1.8]	[1.0–2.2]	[2.1–4.3]	[1.5–3.0]	[2.0–3.8]	[1.1–8.1]
VRS 2	1.8 (0.2)	2.6 (0.8)	6.6 (3.4)	3.5 (1.4)	4.8 (1.6)	9.6 (4.2)
"Hurting"	[1.7–2.2]	[1.3–3.4]	[1.9–10.4]	[2.1–5.0]	[2.5–7.3]	[2.2–13.3]
VRS 3	2.3 (0.4)	4.0 (1.4)	9.6 (4.5)	5.4 (2.1)	7.5 (2.0)	12.5 (4.7)†
"Hurting a lot"	[1.7–2.8]	[2.1–6.0]	[3.0–15.8]	[3.1–7.1]	[4.6–10.5]	[3.4–15.7]
VRS 4	3.0 (0.3)	5.4 (1.4)	12.8 (5.4)†	6.9 (1.9)	9.8 (3.3)†	14.3
"Agony"	[2.5–3.5]	[3.2–7.3]	[9.6–19.0]	[4.8–9.0]	[5.5–14.7]	[one subject]
Release	3.7 (0.7)	6.4 (2.0)	13.2 (4.7)‡	7.6 (2.3)	10.8 (2.9)†	14.6
"Exhaustion"	[3.0–5.0]	[3.5–9.2]	[9.6–19.0]	[5.3–11.1]	[7.3–15.3]	[one subject]

None of our six subjects could sustain a force of 40 N for the target time using either the extended or flexed arm. Only one subject was able to sustain 30 N for the target time and then only using the extended arm. At 20 N, the lowest force studied, two subjects achieved the target time using the flexed arm, and five subjects achieved it using the extended arm. All subjects who achieved the target time did so at the limit of physical tolerance. The use of the extended arm consistently prolonged times to release.

Comment

We chose to vary the height of the model in relation to the subject's stature to obtain comparable mechanical advantage. The extended position with the arm locked at the elbow is unlikely to be encountered in routine practice unless specific measures are undertaken to achieve it. However, the flexed position is more clinically representative, as the cricoid cartilage of a patient recumbent on a hospital trolley lies at approximately the level of the elbow joint for a subject of average height (standard trolley height 90 cm; neck diameter 10–15 cm; elbow joint height 110–113 cm for a subject of average (173 cm) height—personal observations). A target of 20 min was chosen to set an achievable task that would not demoralize our study group.

We have shown that, with the arm flexed to 90°, it is physically possible to sustain 30 and 40 N for only a short time (2–4 min). We found that 20 N could be sustained for longer periods (10–20 min) but even at this force, those subjects that achieved or approached the target time did so at the limits of their physical tolerance.

We found that the use of the extended arm approximately doubled times to pain and fatigue, but the operator's hand in the extended position may obstruct the laryngoscope handle and so this position cannot be recommended for routine use. However, adopting this position would seem sensible when intubation attempts have ceased and there is continuing requirement for cricoid pressure. This position is best achieved by the assistant standing on a raised platform.

The rapid onset and degree of pain was another unexpected finding of this study. We doubt the ability of a subject in pain to maintain protective force, and we believe that times to pain (VRS 3) are clinically relevant. Furthermore, when the safety of the technique is being considered, it is the shortest times to unbearable pain or fatigue that are important. For example, with the arm flexed at 30 N, the lowest recommended force, the shortest times to pain (VRS 3) and release were only 2.1 and 3.5 min, respectively. These times are commensurate with uncomplicated intubation but not, for instance, with the maximum duration of action of succinylcholine in the obstetric population.

We found that 20 N can be sustained for a more useful length of time, but what level of protection does it provide? This may be estimated from the studies of Vanner and colleagues which concluded that forces of 40 N[2] and 30 N[3] were optimum. The criterion used to judge optimum force in these studies was the ability of applied cricoid force (ACF) to generate oesophageal pressures *in excess* of the *median* value for upper oesophageal sphincter pressure in awake subjects. However, in cadavers tested at 20 N ACF,[3] the onset of regurgitation occurred at oesophageal pressures that ranged between 26 and 60 mm Hg. In anaesthetized patients, 20 N ACF[2] generated oesophageal pressures of 10–90 mm Hg (25th percentile 30 mm Hg; median 42 mm Hg). The ability of 20 N ACF to generate oesophageal pressures of this magnitude would seem to offer considerable protection. Intra-gastric pressure (IGP) is a central factor for regurgitation but its relative influence has largely been ignored. The range of IGP encountered in clinical practice is a more logical criterion on which to judge the protection offered by any given ACF. However, there is insufficient published information on IGP and anaesthesia to estimate the protection offered by 20 N ACF.

In this study, subjects received direct feedback of the applied force. Performance in less ideal conditions must be more questionable. There is no practical method of measuring ACF in clinical practice. However, we recommend that all anaesthetists and anaesthetic assistants receive practical training in the application of target forces and regularly update these skills. A low cost training device can be constructed using a set of weighing scales.

Our findings are relevant to the management of cricoid pressure in the context of failed intubation. To expect a single subject to sustain effective cricoid pressure for more than approximately 10 min, even at forces below those currently recommended, would appear unreasonable. A changeover of personnel could be used to extend this time, but would present many practical difficulties. We have reviewed recent failed intubation guidelines[5,6] and found none that considers the difficulty of maintaining cricoid pressure over time. We can offer no simple solution to this dilemma but hope a new understanding of the limits of the protection provided by cricoid pressure will aid decision making in extreme circumstances.

We urge that in future, in failed intubation guidelines, the limitations of cricoid pressure are made explicit.

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Gastro-oesophageal reflux with the laryngeal mask during day-case gynaecological laparoscopy

H. J. Skinner, B. Y. M. Ho and R. P. Mahajan

Summary

We have evaluated if breathing spontaneously via a laryngeal mask airway is associated with a higher risk of gastro-oesophageal reflux compared with positive pressure ventilation via a laryngeal mask airway in 40 patients undergoing day-case gynaecological laparoscopy. Patients were allocated randomly to receive either positive pressure ventilation or breathe spontaneously via a laryngeal mask airway. Using continuous oesophageal pH monitoring, three patients in the ventilated group and one in the spontaneous breathing group had gastro-oesophageal reflux (P=0.29). We found no evidence to suggest that breathing spontaneously via a laryngeal mask airway increased the risk of gastro-oesophageal reflux compared with positive pressure ventilation in this group of patients. (*Br. J. Anaesth.* 1998; **80**: 675–676)

Keywords: equipment, masks anaesthesia, surgery, laparoscopy; gastrointestinal tract, reflux

Even though patients undergoing gynaecological laparoscopy are considered to be at a particular risk of gastric aspiration,[1] the laryngeal mask airway (LMA) has been used successfully with a low incidence of regurgitation.[2] However, Owens and colleagues[3] have shown the use of the LMA to be associated with an incidence of gastro-oesophageal reflux (GOR) of 54% in spontaneously breathing patients. They suggested that a decrease in lower oesophageal sphincter barrier pressure by the LMA[4] together with an increase in resistance to breathing with a greater negative intrathoracic pressure during inspiration, may promote GOR. Roberts and Goodman[5] did not detect any episode of GOR in 63 patients who underwent gynaecological laparoscopy. All of their patients underwent ventilation via a tracheal tube. There is a paucity of data comparing the effect of spontaneous breathing with positive pressure ventilation (PPV) using the LMA in patients undergoing gynaecological laparoscopy. In this study, we have determined the incidence of GOR with the LMA in this "at risk" group of patients and investigated if breathing spontaneously was associated with a higher risk of GOR compared with PPV.

Methods and results

After obtaining approval from the hospital Ethics Committee and written informed consent, we studied 40 patients, ASA I or II, undergoing day-case gynaecological laparoscopy. Women with a history of reflux or hiatus hernia, those receiving medication that may affect gastric pH or motility, and those with a body mass index greater than 30 kg m^{-2} were excluded.

After placement of routine monitoring devices, anaesthesia was induced with alfentanil 10 μg kg^{-1}, propofol 2–3 mg kg^{-1} and glycopyrrolate 100 μg. While patients were apnoeic after induction, anaesthesia was maintained by gentle manual ventilation with 1–2% isoflurane and 66% nitrous oxide in oxygen. An oesophageal pH electrode was passed by the investigator before insertion of a size 3 LMA. Thereafter patients were allocated randomly to one of two groups to breathe spontaneously or receive PPV via the LMA. Patients in the PPV group received vecuronium 0.07 mg kg^{-1} and underwent ventilation to normocapnia (Datex, Capnomac) with the Manley ventilator. Peak airway pressures were limited to 20 cm H_2O by adjusting tidal volume. Airway pressures were measured at the junction between the LMA and breathing system with a low pressure transducer and Datex monitor. Patients in the spontaneously breathing group were assisted manually until they resumed a regular breathing pattern. I.v. morphine, up to 0.15 mg kg^{-1}, and rectal diclofenac 100 mg were given to provide additional analgesia. No antiemetic was given until conclusion of the study.

Duration of anaesthesia, duration of pneumoperitoneum, peak intra-abdominal insufflation pressure and degree of head-down tilt were recorded. At the end of operation, neuromuscular block was antagonized in the PPV group with neostigmine 2.5 mg and glycopyrrolate 0.5 mg. The LMA, together with the pH electrode, were removed when patients were awake.

The monocrystalline antimony pH electrode (Synectics Medical Ltd) was calibrated before each set of measurements. The electrode was passed nasally and advanced under direct laryngoscopy until gastric pH was recorded, as described previously.[5] It was then withdrawn to the gastro-oesophageal junction (as indicated by a sudden increase in pH) and secured another 4–5 cm above the gastro-oesophageal junction. Continuous oesophageal pH measurements were started when the electrode was positioned correctly

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Table 1 Patient characteristics (mean (SD or range)) in the two groups

	Spontaneous breathing (n=20)	PPV (n=20)	P
Age (yr)	33 (24–45)	33 (23–42)	
Body mass index (kg m^{-2})	25 (3.4)	25 (2.6)	
Gastric pH	1.4 (0.3)	1.3 (0.4)	
Duration of anaesthesia (min)	29 (12)	24 (4.7)	
Duration of pneumoperitoneum (min)	14 (12)	8.8 (3.6)	
Peak intra-abdominal insufflation pressure (mm Hg)	15 (2.9)	12 (3.0)	0.015
Peak airway pressure (cm H_2O)		15 (1.6)	
Degree of head-down tilt	14 (2.2)	15 (2.0)	
End-tidal CO_2 (kPa)	7.0 (0.7)	5.2 (0.4)	<0.001
No. of patients with GOR	1 (5%)	3 (15%)	0.29

and recorded throughout operation. The anaesthetist was blinded to the pH measurements during operation. A reflux episode was defined as a decrease in pH to less than 4. The recordings were stored in the Digitrapper MD monitoring device and analysed subsequently using Gastrosoft software (Synectics Medical Ltd).

The quoted incidence of reflux or regurgitation in gynaecological laparoscopy with PPV via a tracheal tube is less than 5%.[1 5] Assuming an incidence of 10% with PPV via an LMA and given the reported incidence of GOR of more than 50% when breathing spontaneously via an LMA, power analyses suggested that 20 patients were required in each group to have more than 80% chance of showing a difference between the groups at $\alpha<0.05$. Patient data were compared using the unpaired t test. The incidence of reflux was analysed with Fisher's exact test. $P<0.05$ was regarded as statistically significant.

There were no significant differences between the groups in patient characteristics, duration of anaesthesia, duration of pneumoperitoneum and degree of head-down tilt (table 1). Intra-abdominal insufflation pressure was higher in the group breathing spontaneously. In no patient was there a significant audible leak around the LMA cuff. Satisfactory chest movements were attained in all patients during assisted and mechanical ventilation.

There was no clinical evidence of regurgitation in any patient. However, using continuous oesophageal pH monitoring, three patients in the PPV group and one patient breathing spontaneously had evidence of GOR (P=0.29, Fisher's exact test). Of the three patients in the ventilation group who had evidence of reflux, two had episodes of reflux during the period of pneumoperitoneum. The other patient had hiccups on induction and a reflux episode 3 min later. The patient breathing spontaneously had a reflux episode just after the pneumoperitoneum had been relieved.

Comment

The LMA has been shown to decrease lower oesophageal sphincter barrier pressure.[4] A combination of head-down and lithotomy position, and pneumoperitoneum used during gynaecological laparoscopy is thought to render these patients at a higher risk of regurgitation.[1]

We found an incidence of GOR of 10% with the LMA in this patient population. This is much lower than the incidence of more than 50% reported by Owens and colleagues[3] in patients undergoing a variety of minor surgical procedures, even when accounting for the reflux events that occurred in the recovery unit after the LMA had been removed in their patients. However, there is an adaptive increase in lower oesophageal sphincter pressure in response to increased intra-abdominal pressure during laparoscopic surgery[6] which may have accounted for the relative low incidence of GOR in our study. We discontinued recordings at removal of the LMA as patients were thought to be able to protect their own airway at this point.

Righini and colleagues[7] confirmed that the LMA significantly increased inspiratory airway resistance because of the configurational changes occurring when the LMA is *in situ*. Greater negative intrathoracic pressures may be generated during the inspiratory phase of breathing via the LMA. This has been forwarded as a possible reason for the high incidence of GOR in spontaneously breathing patients.[3] However, we detected a lower incidence of GOR in the group breathing spontaneously (5%) compared with the PPV group (15%). The difference was not statistically significant. Based on these results and the power of our study, we conclude that breathing spontaneously via an LMA did not increase the risk of GOR compared with PPV.

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Clinical assessment of the single use laryngeal mask airway—the LMA-Unique

C. VERGHESE, J. BERLET, A. KAPILA AND R. POLLARD

Summary

We conducted a clinical comparison of the laryngeal mask airway (LMA) and the new single use PVC LMA (LMA-Unique) in 100 fasted adult patients undergoing elective surgery. Patients were allocated to one of two groups: group 1 (n=50) was managed by two consultants and group 2 by two trainee anaesthetists. Airway management was randomized prospectively within each group, and cuff pressure in both devices was maintained at a maximum of 50 mm Hg with upward size substitution if leaks persisted during intermittent positive pressure ventilation (IPPV). Insertion with the recommended technique was successful in all patients (85 first attempt). One patient (group 1) required four attempts for insertion of the LMA-Unique and in one patient (group 2) the LMA-Unique was replaced by a tracheal tube because of persistent leaks during IPPV. In 99 patients IPPV was uneventful. The adjusted mean volume of air for cuff inflation in the LMA-Unique was significantly less in group 1 (P=0.0013). At fibreoptic laryngoscopic examination, the vocal cords or arytenoids, or both, could be seen in 92% of patients in group 1 and in 90% of patients in group 2. Immediate throat soreness was reported in four patients in group 1 and in seven in group 2. The results suggest that the LMA-Unique was similar in clinical performance to the LMA. (*Br. J. Anaesth.* 1998; **80**: 677–679)

Keywords: equipment masks anaesthesia; intubation tracheal; ventilation intermittent positive pressure

The laryngeal mask airway (LMA) has become an increasingly popular alternative to the face mask or tracheal tube for securing the airway in fasted patients undergoing elective surgery under general anaesthesia, for immediate airway support in cardiopulmonary resuscitation (CPR) by nurses trained in its use and is included in the European Resuscitation Council advanced airway management algorithm.[1-4] Calder and colleagues reported on its use in failed intubations[5] and Benumof recommended its use in the ASA difficult airway algorithm.[6]

The LMA may be re-used up to 40 times after recommended sterilization procedures.[2] However, for pre- and in-hospital CPR and in the high infection risk patient, a disposable LMA may be preferred.

The LMA-Unique was introduced in September 1997 as a "single use"/disposable device at approximately one-third of the cost of an LMA. The cuff, backplate, airway tube and pilot balloon of the LMA-Unique are manufactured from clear medical grade PVC (ISO 10993 biocompatibility standard). The airway tube is clear, semi-rigid and more curved than the softer silicone airway tube of the LMA, but is otherwise similar in appearance to the LMA (fig. 1). The LMA-Unique is supplied sterile and cannot withstand autoclaving.

In this study, we have compared the LMA-Unique with the LMA for ease of insertion, alignment with the laryngeal inlet (verified using fibreoptic laryngoscopy), IPPV and incidence of immediate sore throat.

Methods and results

After obtaining approval from the local Ethics Committee and written informed consent, we studied 100 fasted adult patients (ASA I–III) undergoing elective surgery requiring general anaesthesia with neuromuscular blocking agents and intermittent positive pressure ventilation (IPPV). Patients were allocated to one of two groups (n=50): group 1 was managed by two consultant anaesthetists and group 2 by two trainee anaesthetists. Pregnant, non-fasted and patients with symptomatic gastro-oesophageal reflux disease were excluded. Patients in each group were randomized prospectively for airway management with the LMA or LMA-Unique (adult sizes 4 and 5) using a randomized sealed envelope technique.

Perioperative monitoring included non-invasive arterial pressure, pulse oximetry, continuous ECG, end-tidal carbon dioxide and end-tidal MAC (Datex AS/3 ADU, Datex Corporation, Finland). General anaesthesia was induced with fentanyl 1–1.5 μg kg^{-1} and propofol 2–3 mg kg^{-1}. Neuromuscular block was established with atracurium 0.5 mg kg^{-1} and after loss of response to peripheral nerve stimulation, either the LMA or LMA-Unique was inserted. The insertion technique was standardized to that recommended for LMA insertion.[2] After insertion, cuff inflation of either device was to a "just-seal" pressure or up to a maximum of 50 mm Hg, measured with a simple hand-held aneroid manometer (Yamasa, Harvey Medic, Surrey). The volume of air used was recorded, and if leaks persisted on gentle manual ventilation, a larger sized device was substituted. Cuff pressure was monitored continuously and maintained at 50 mm Hg or less, by removal or addition of small volumes of air.

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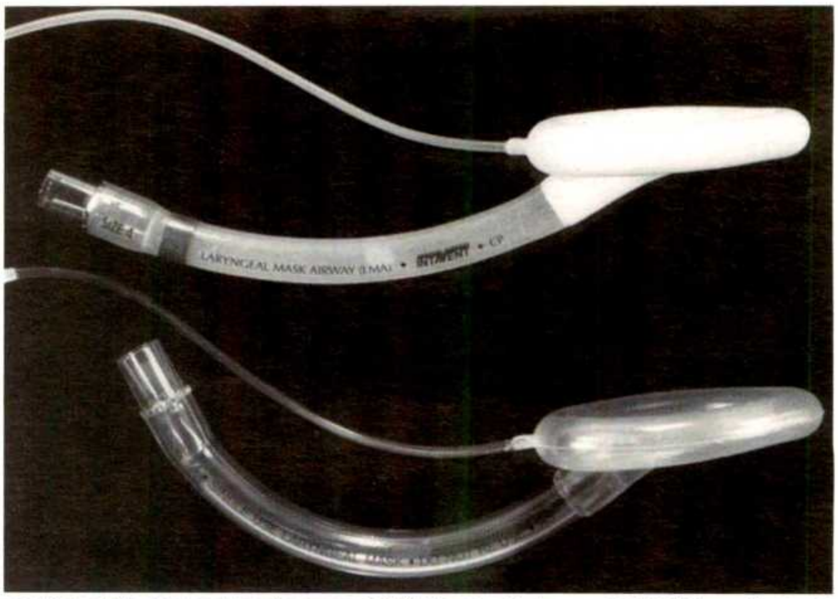

Figure 1 Comparison of the laryngeal mask airway (LMA) (top) with the new LMA-Unique (bottom), a "single use"/disposable device manufactured from clear PVC.

Anaesthesia was maintained with 1–2% isoflurane and nitrous oxide in oxygen. Atracurium was given to abolish responses to peripheral nerve stimulation. Mechanical ventilation was volume controlled and time cycled with tidal volumes (5–8 ml kg^{-1}) set to maintain peak inspiratory pressures of less than 20 cm H_2O and ventilatory frequency adjusted to maintain end-tidal carbon dioxide (PE'_{CO_2}) at 4.5–5.0 kPa. In the perioperative period, a fibreoptic laryngoscope (Olympus LF-2, Keymed, Essex) was passed through a swivel elbow (Intersurgical) into the device, so that the tip was just above the cuff tears. The view was scored as described previously.[7]

Neuromuscular block was antagonized with glycopyrrolate 0.5 mg and neostigmine 2.5 mg. Patients breathed spontaneously until protective reflexes returned and the device was then removed with the cuff inflated. The presence of blood was recorded.

On discharge from the recovery room, patients were asked if they had a sore throat and responses were recorded as nil, mild, moderate or severe (table 1). All data were recorded on a simple form and transferred onto a spreadsheet (Microsoft EXEL 7.0). Statistical analysis was with SAS 6.0.

There were no failures on inserting either device. One substitution upwards took place in the LMA group in group l, and in one LMA and LMA-Unique in group 2. These three patients required only one attempt for re-insertion (table 1). The male patient in group 2 in whom a tracheal tube replaced the size 5 LMA-Unique was not included in the data analysis.

Chi-square analysis demonstrated that there was no association between use of the LMA or LMA-Unique, and experience of the user, incidence of sore throat or fibreoptic laryngoscopy score. Analysis of variance showed that the mean volume of air used to inflate the cuff of the LMA-Unique was significantly lower in group 1 (P=0.0013). None of the patients showed clinical signs of regurgitation or aspiration of gastric contents during the study.

Table 1 Patient characteristics (mean (SD) [range] or number) in the two groups. FOL=Fibreoptic laryngoscopy

	Group 1 (34 males)		Group 2 (18 males)	
	LMA	LMA-Unique	LMA	LMA-Unique
Weight (kg)	79.67 (11.50) [60–112]	78.08 (14.53) [50–105]	76.35 (19.95) [55–118]	74.03 (16.65) [54–122]
Insertion attempts				
1	23	22	20	20
2	1	3	5	3
3		0	1	1
4		1		
Mean volume of air in cuff (ml)	17.78	17.31	19.92	24.92
Duration of airway *in situ* (min)	75.20 (48.28)	84.80 (37.92)	62.46 (19.13)	80.52 (38.05)
FOB Score				
1=only vocal cords seen	11	13	13	16
2=cords and/or arytenoids	11	11	9	6
3=only epiglottis seen	1	2	4	1
4=other (e.g LMA cuff, pharynx, etc)	1	0	0	0
Blood seen on device	4	5	5	4
Sore throat				
No pain	21	25	24	18
Little pain	3	0	2	4
Moderate pain	0	1	0	1
Moderate to severe pain	0	0	0	0

Comment

Our initial impression of the LMA-Unique was that although it was similar in shape to the LMA, it was stiffer. We considered that the relative stiffness of the tubular portion combined with the hardness of the backplate tip might contribute to difficulty in insertion, a higher incidence of trauma during insertion and a greater incidence of sore throat. Brimacombe documented early and late learning curves in the use of the LMA, and therefore we used two groups to assess the new device.[8] Ease of insertion of both devices with the recommended insertion technique for the LMA was similar both within and between groups, and was successful in all patients. The only patient requiring four attempts for insertion of the LMA-Unique was a 48-yr-old female patient, 1.68 m tall, weighing 67 kg, with a fibreoptic laryngoscopy score of I, who had blood present on the cuff with no immediate sore throat. $P\mathrm{E}'_{\mathrm{CO}_2}$ was maintained at 4.0–5.0 kPa in all 99 patients at ventilatory frequencies of 10–14 bpm. Chi-square analysis of fibreoptic laryngoscopy view scores showed no association with the type of device used, incidence of sore throat or experience of the user.

Direct questioning would increase the likelihood of complaints of sore throat. However, 92% of patients in group 1 and 85.7% in group 2 reported no throat soreness.[9] Duration of placement did not contribute to the incidence of sore throat. The low incidence of sore throat in both groups may have resulted from careful attention to the insertion and fixation technique, use of neuromuscular blocking agents and maintenance of cuff pressures at less than 50 mm Hg.[10] Lower volumes of air were required to achieve a seal in the LMA-Unique compared with the LMA in group 1 and may reflect the lower compliance of PVC and the experience of the users. At low cuff pressures the device moulds itself to laryngeal structures whereas at higher pressures the cuff imposes its contours on laryngeal structures. A larger study may establish if smaller volumes of air need to be used to inflate the cuff of the LMA-Unique compared with the LMA to achieve "just seal" pressures.

The presence of blood on the cuff after removal was used as an indicator of tissue trauma and our data showed a low incidence with both devices after removal, which was similar between and within groups.

In summary, this study suggests that the LMA-Unique was similar to the LMA for ease of insertion, alignment with the laryngeal inlet, ventilation of the lungs of paralysed patients requiring IPPV and incidence of immediate sore throat.

Acknowledgements

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British Journal of Anaesthesia 1998; **80**: 680–681

Comparison between extradural infusion of ropivacaine or bupivacaine for the prevention of postoperative pain after total knee arthroplasty

T. MULDOON, K. MILLIGAN, P. QUINN, D. C. CONNOLLY AND K. NILSSON

Summary

We have compared the analgesia and motor block produced by extradural infusions of ropivacaine and bupivacaine after total knee arthroplasty. Fifty-two patients received 8 ml h^{1} of either 0.2% ropivacaine or 0.2% bupivacaine by extradural infusion for 24 h after operation. Analgesia was assessed by postoperative visual analogue scale (VAS) and morphine consumption. At rest these were low in both groups; median VAS was 0–13.3 mm for the ropivacaine group and 0–0.5 mm for the bupivacaine group. Over the 24 h of the infusion, the estimated (ropivacaine bupivacaine) difference in wound pain at rest was 5.6 mm (P=0.017) and on passive movement 11.6 mm (P=0.016). Median morphine consumption was 30.7 mg in the ropivacaine group and 20.5 mg in the bupivacaine group. In the ropivacaine group, 50% of patients compared with 19% in the bupivacaine group had no motor block 2 h after operation, increasing to 88% for ropivacaine and 56% for bupivacaine by 24 h. Bupivacaine produced significantly more frequent and intense motor block over the 24 h (P=0.015). (*Br. J. Anaesth.* 1998; **80**: 680–681)

Keywords: anaesthetics local, bupivacaine; anaesthetics local, ropivacaine; analgesic techniques, extradural; pain, postoperative; surgery, orthopaedic

Ropivacaine has similar pharmacokinetic and pharmacodynamic properties to bupivacaine[1] but has been shown to have lower cardiac and CNS toxicity[2] and greater separation between sensory and motor block.[3] A previous study comparing 0.1, 0.2 and 0.3% ropivacaine after orthopaedic surgery demonstrated that 0.2% ropivacaine provided good analgesia with minimum motor block.[4]

We have compared analgesic efficacy, and sensory and motor block of 0.2% bupivacaine and 0.2% ropivacaine administered at 10 ml h^{-1} by extradural infusion after total knee arthroplasty.

Methods and results

After obtaining approval from the Ethics Committee and informed patient consent, we studied 52 healthy patients, aged 49–75 yr, weight 50–105 kg, undergoing elective total knee arthroplasty.

Before operation, patients were instructed on the use of a visual analogue scale (VAS) ruler (Biomedical Engineering) consisting of a 100-mm horizontal line marked "no pain" (0 mm) and "worst possible pain" (100 mm), and were shown how to use an Abbott Lifecare PCAS pump. Patients were excluded if there was any contraindication to extradural anaesthesia or a potential inability to co-operate with the clinical assessments.

Patients were allocated randomly, in a double-blind manner, to receive either bupivacaine or ropivacaine supplied in identical ampoules. Temazepam 20 mg orally was given 2 h before surgery. All oral analgesics were stopped on the night before surgery.

In theatre, a 16-gauge Veflon was inserted, and routine monitoring commenced; dextran 70 500 ml and Hartmann's solution 500 ml were administered. An extradural catheter was inserted at the L2–4 interspace and a 3-ml test dose of 2% lidocaine with epinephrine was administered. Five minutes later 15 ml of either 0.5% bupivacaine or 0.5% ropivacaine were injected over 5 min. The level of sensory block was assessed every 5 min with ice. When this reached T10 anaesthesia was induced with propofol 1–2 mg kg^{-1}. A laryngeal mask was inserted and anaesthesia was maintained with 1–2% isoflurane and 60% nitrous oxide in oxygen.

On completion of surgery, an extradural infusion (8 ml h^{-1}) of either 0.2% bupivacaine or 0.2% ropivacaine was commenced and continued for 24 h. A PCAS was connected and set to deliver morphine 1-mg bolus doses with a 5-min lockout period.

After operation, patients were transferred to a high dependency unit for routine monitoring. Wound pain at rest and on passive extension was assessed every 2 h using a VAS marked 0–100 mm, and morphine consumption was recorded. Sensory block was assessed every 2 h by loss of sensation to ice and motor block was assessed in the non-operated leg every 2 h using a modified Bromage score.[5] In addition, patients scored overall quality of analgesia using a five-point scale.

Morphine consumption, VAS scores, overall quality of treatment scores, and sensory and motor block were compared using non-parametric Wilcoxon

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Table 1 Patient characteristic (mean (SD or range)) and median pain scores (VAS) greater than 30 mm at rest and during mobilization at times 0–4, 0–8 and 0–24 h

	Ropivacaine group (*n*=26)	Bupivacaine group (*n*=26)
Age (yr)	65.7 (49–75)	68.2 (54–74)
Height (cm)	163 (7.5)	164.5 (8.3)
Weight (kg)	78.2 (13.7)	78.7 (11.1)
VAS >30 mm at rest		
0–4 h	2	2
4–8 h	8	3
8–24 h	15	9
VAS >30 mm on mobilization		
0–4 h	3	2
4–8 h	11	10
8–24 h	21	14

(mid) rank sum tests. *P* values reported correspond to two-tailed tests; *P* values less than 5% were considered significant. No correction for multiplicity was performed.

A summary measure (AUCM) was used for analysis of the study, calculated as follows. First, the area under the curve (AUC) based on repeated measurements during a time interval was calculated using the trapezoidal rule (extended to both of the end points by extrapolation if necessary). The summary measure considered was then defined as this AUC divided by the length of time on which it is based, so that it had the same scale as the underlying repeated measurements.

The two groups, each comprising 26 patients, were similar in patient characteristics (table 1). Median pain scores at rest in the ropivacaine group were 0–13.3 mm while those in the bupivacaine group were 0–0.5 mm. Pain scores on mobilization were higher in the ropivacaine group than in the bupivacaine group. There were no significant differences in the number of patients reporting a pain score at rest or on movement of >30 mm during any of the intervals 0–4, 4–8 or 8–24 h (table 1); however, at 8–24 h, more patients in the ropivacaine group scored their pain on movement as >30 mm (*P*=0.040).

Comparisons of AUCM for pain at rest and on movement were performed between the ropivacaine and bupivacaine groups, at times 0–4, 4–8 and 8–24 h. At 0–4 and 4–8 h, there were no significant differences between the groups at rest or on movement. During the interval 8–24 h there was a significantly higher AUCM score in the ropivacaine group, both at rest (*P*=0.031) and on movement (*P*=0.022). At rest the estimated (ropivacaine–bupivacaine) difference over that time was 6.4 mm and on movement 12.9 mm.

Upper median segmental spread of sensory block after 2 h was T7–T6 for ropivacaine and T6–T5 for bupivacaine. After 24 h of infusion, median upper sensory spread was L2–L1 for both groups. Lower median segmental spread was consistently S1 in each group.

Motor block was assessed in the non-operated leg; it decreased in both groups during the study. By 2 h after operation, 50% of the ropivacaine group compared with 19% in the bupivacaine group were free from motor block. After 24 h, this had increased to 88% and 56%, respectively. Hence bupivacaine produced more frequent and intense motor block. The AUCM for motor block was calculated at times 0–4, 4–8 and 8–24 h. Patients in the ropivacaine group had a lower degree of motor block than those in the bupivacaine group. There was a significantly lower AUCM in the ropivacaine group than in the bupivacaine group at all three times: 0–4 (*P*=0.041), 4–8 (*P*=0.032) and 8–24 h (*P*=0.012).

Median morphine consumption was 30.7 mg (interquartile range 17–57 mg) in the ropivacaine group and 20.5 mg (interquartile range 8–40 mg) in the bupivacaine group (ns). The overall quality of analgesia was similar in both groups and was rated as good or excellent by 77% of patients in the ropivacaine group and by 80% in the bupivacaine group.

Comment

This study showed that extradural bupivacaine or ropivacaine 16 mg h^{-1} combined with PCA morphine provided effective analgesia after total knee replacement.

The ropivacaine group had slightly higher VAS scores but the mean value of the difference between groups was only 5.6 mm at rest and 11.6 mm on passive movement and may not reflect a significant difference clinically. Ropivacaine in equal concentration and dose produced much less motor block than bupivacaine.

We feel that mixtures of opioids and ropivacaine warrant study, as the addition of opioid may improve the analgesic efficacy of 0.2% ropivacaine while maintaining the beneficial motor characteristics. It may also be possible to lower the concentration of ropivacaine, thereby further reducing motor block while maintaining adequate analgesia.

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Repeated vital capacity manoeuvres after cardiopulmonary bypass: effects on lung function in a pig model

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Summary

Respiratory failure following cardiopulmonary bypass (CPB) is a major complication after cardiac surgery. A vital capacity inflation of the lungs, performed before the end of CPB, may improve gas exchange, but the necessity to repeat it is unclear. Therefore, we studied 18 pigs undergoing hypothermic CPB. A vital capacity manoeuvre (VCM) was performed in two groups and consisted of inflating the lungs for 15 s to 40 cm H_2O at the end of CPB. In one group, VCM was repeated every hour. The third group served as controls. Atelectasis was studied by CT scan. Intrapulmonary shunt increased after bypass in the controls and improved spontaneously 3 h later without returning to baseline values. From 3 to 6 h after CPB, there was no more improvement and more than 10% atelectasis remained at 6 h. In contrast, the two groups treated before termination of CPB with VCM showed only minor atelectasis and no abnormal changes in gas exchange directly after bypass or later. We conclude that the protective effect of VCM remained for 6 h after bypass, and there was no extra benefit on gas exchange by repeating the VCM. (*Br. J. Anaesth.* 1998; **80**: 682–684)

Keywords: anaesthesia general; lung atelectasis; heart cardiopulmonary bypass; hypoxaemia; lung shunting; lung function; pig

Postoperative respiratory insufficiency is a major complication after cardiac surgery with cardiopulmonary bypass (CPB).[1] In a recent study, using a pig model, we found that CPB caused more atelectasis (35% of the total lung area) than in a control group without CPB (2%).[2] We also found that a vital capacity manoeuvre (VCM) (inflating the lungs to 40 cm H_2O before the end of CPB) prevented atelectasis and gas exchange impairment after CPB,[3] but we only followed changes for 1 h after termination of bypass. In healthy patients during general anaesthesia, VCM has an effect limited in time, and atelectasis can recur.[4] We hypothesized that atelectasis also recurs after CPB if VCM is applied at the end of bypass.

Therefore, in this study we assessed the duration of benefit of VCM performed just before termination of bypass and investigated if there was any advantage in repeating VCM.

Methods and results

After obtaining approval from the Animal Research Ethics Committee of Uppsala University, we studied 18 pigs subjected to CPB. In six pigs VCM was performed 5 min before the end of bypass (group VCM 1); in another six pigs, VCM was performed 5 min before termination of CPB and then repeated every hour (group VCM 6). The six remaining pigs were treated as controls and VCM was not performed (control group). VCM consisted of inflating the lungs to 40 cm H_2O for 15 s. The same technique was applied to the two VCM groups with an opened chest at the end of bypass, and after bypass with a closed chest in group VCM 6.

After induction of general anaesthesia, tracheal intubation was performed and artificial ventilation instituted using a volume-cycled ventilator. Tidal volume was 10 ml kg^{-1} and ventilatory frequency was adjusted to maintain end-tidal carbon dioxide partial pressure at 5.2–5.6 kPa, with a positive end-expiratory pressure of 4 cm H_2O. The ventilator settings were maintained constant throughout the procedure. The inspired oxygen fraction was 0.4 (balance nitrogen).

A median sternotomy was performed, and the pericardium and both pleura were opened. Perfusion was conducted using a non-pulsatile pump primed with Ringer's acetate solution 600 ml and 15% mannitol 200 ml. After the beginning of CPB, hypothermia to 30°C was induced, ventilation was stopped and the airway opened to atmosphere. The aorta was clamped and cardioplegic solution injected until cardiac arrest (total duration of cardiac ischaemia=45 min). During CPB, chest drains were inserted in both pleura.

Before separation from bypass, the pigs were rewarmed for 40 min. Total duration of CPB was 90 min. At the end of bypass, all pump prime was returned to the animals via the aortic cannula. Fifteen minutes before termination of bypass, ventilation was reinstituted at half the tidal volume value. Just before termination of bypass, VCM was performed in the two VCM groups.

Measurements consisted of blood-gas tensions, standard haemodynamic variables, extravascular lung water and respiratory mechanics.[2] Intrapulmonary

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Table 1 Haemodynamic and respiratory variables (mean (SD)). CPB=Cardiopulmonary bypass, VCM=vital capacity manoeuvre, $P_a$aw=end-inspiratory pressure, MPAP=mean pulmonary arterial pressure. $^*P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ compared with baseline; $^\dagger P<0.05$, $^{\dagger\dagger}P<0.01$, $^{\dagger\dagger\dagger}P<0.001$ compared with the control group; $^\ddagger P<0.05$, $^{\ddagger\ddagger}P<0.01$ compared with the VCM 1 group

	Control group		VCM 1 group		VCM 6 group	
	Baseline	6 h after CPB	Baseline	6 h after CPB	Baseline	6 h after CPB
$P_a$aw (cm H_2O)	16.0 (1.0)	19.7 (1.4)***	15.7 (1.4)	19.2 (1.4)*	15.9 (0.5)	16.5 (0.8)†††‡‡
Compliance (ml cm H_2O^{-1})	26.2 (4.4)	16.3 (3.3)***	24.4 (3.8)	20.2 (2.1)*†	24.5 (2.8)	24.2 (3 8)†††‡
MPAP (mm Hg)	17.3 (2 7)	24 7 (1.6)**	17 8 (0.8)	24.0 (3.9)*	16.5 (1.9)	19.8 (1.0)*††‡‡
Shunt (%)	4.2 (1.6)	8.8 (5.5)	4.3 (3 1)	3.8 (1.4)†	4.9 (3.1)	2 5 (2.0)†
Pa_{O_2}/Fi_{O_2} (mm Hg)	476 (55)	349 (105)*	484 (98)	482 (47)†	462 (53)	502 (76)†
Atelectasis (%)		11.8 (7.3)		1.8 (2.2)††		1.3 (1 2)††
Poorly aerated lung (%)		36.1 (13.5)		17.0 (6.4)††		16.6 (7.0)††

shunt was calculated using standard formulae. A delay of 30 min was allowed after the surgical preparation before baseline measurements were made. Because of the time necessary to remove the CPB cannulae and close the chest, the first measurements after bypass were not obtained until 20–30 min after separation from bypass. The same measurements were repeated at 3 and 6 h after CPB. After the last series of measurement, the pigs were moved to the CT scan laboratory. One CT scan was performed at end-expiration, 0–1 cm above the diaphragm. Non-aerated lung tissue (atelectasis) was defined as regions with attenuation values between −100 and +100 Hounsfield Units (HU)[5] and poorly aerated lung tissue as regions with values between −500 and −100 HU. The extent of atelectasis and poorly aerated lung tissue was expressed as a percentage of total lung area.

Power analysis indicated that six pigs were needed in each group to detect a 50% decrease in atelectasis by repeated VCM compared with a single manoeuvre, with known SD values in the atelectatic area and reproducibility of the method. Data are presented as mean (SD). Analysis of variance (ANOVA) with Bonferroni–Dunn as the *post hoc* test was used for baseline comparisons. The effect of bypass and different VCM exposures were calculated by ANOVA for repeated measurements. $P<0.05$ was considered significant.

The pigs were similar in weight (controls 31.0 (3.9) kg; group VCM 1 31.8 (3.9) kg; and group VCM 6 29.5 (3.2) kg). After bypass, end-inspiratory airway pressures ($P_a$aw) increased significantly in all groups but was more pronounced in the control group. Three hours after bypass, $P_a$aw was significantly less in group VCM 6 than in the two other groups. Six hours after CPB, $P_a$aw had returned to pre-bypass values only in group VCM 6. Compliance decreased in the control group after bypass and was significantly less than in the two VCM groups. This difference persisted at 3 and 6 h after bypass. Compliance also decreased significantly in group VCM 1 at 3 and 6 h after bypass, and was significantly less than in group VCM 6. There were no significant changes in haemodynamic variables, except for mean pulmonary arterial pressure (table 1).

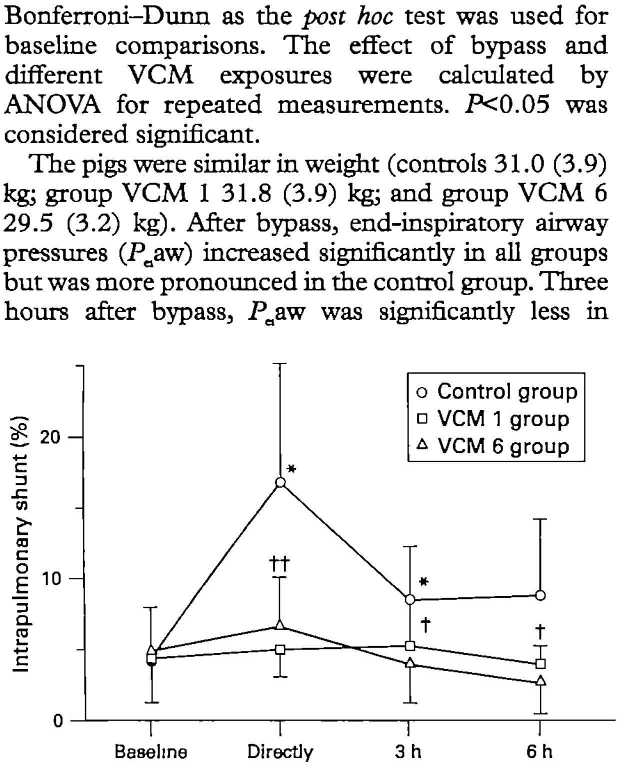

Figure 1 Time course of values of intrapulmonary shunt after cardiopulmonary bypass in the three groups. $^*P<0.05$ compared with baseline, $^\dagger P<0.05$ and $^{\dagger\dagger}P<0.01$ between the control and two other groups.

Intrapulmonary shunt increased markedly (from 4 to 17%; $P<0.05$) (fig. 1) and Pa_{O_2}/Fi_{O_2} decreased (from 476 to 265 mm Hg; $P<0.01$) after bypass in the control group, and not in the two VCM groups. Three hours after bypass, intrapulmonary shunt decreased and Pa_{O_2}/Fi_{O_2} increased in the control group and remained stable thereafter, but the difference compared with the two VCM groups was still significant (table 1, fig. 1). There was no difference in shunt between the two VCM groups.

Atelectasis accounted for more than 10% and poorly aerated lung tissue for 36% of the total lung area in the control group, which was significantly greater ($P<0.01$) than in the two VCM groups (table 1). There was no difference between the two VCM groups in the amount of atelectasis and poorly aerated lung.

Comment

We have shown previously in a pig model that VCM performed just before termination of CPB is effective in preventing atelectasis and gas exchange impairment after bypass.[3] In this study, the control group demonstrated spontaneous improvement in gas exchange between measurements made directly after termination of bypass and 3 h later (fig. 1). This may indicate that conventional ventilation with a low level of PEEP (5 cm H_2O) slowly reopens partially collapsed lung tissue. However, from 3 to 6 h after the end of bypass there was no more improvement and more than 10% atelectasis remained at 6 h. Thus alveolar recruitment appears to be a slow and limited process with conventional ventilation with PEEP. In contrast, the two groups treated before termination of CPB with VCM showed only minor atelectasis and no abnormal changes in gas exchange directly after bypass or later. Thus the beneficial effect of VCM was still present 6 h after the end of bypass, with less atelectasis and gas exchange impairment compared with the control group. This effect was significant despite the spontaneous improvement in the control group. There was no effect on atelectasis or gas exchange from repeating the VCM every hour but repeated lung inflation improved respiratory compliance.

Although previous workers have investigated the effect of various lung management procedures during CPB, few have followed this effect for some hours. Some found a beneficial effect of CPAP just after CPB[6] but this difference was not evident at 4–8 h after the end of bypass. Boldt and colleagues[7] found that lung water returned to normal 5 h after CPB in all patients except those with no CPAP or CPAP 15 cm H_2O, but shunt and Pa_{O_2} did not return to pre-bypass values in any group. In contrast with these results, our study showed that VCM performed before the end of bypass was effective in preventing postoperative impairment in gas exchange.

We conclude that spontaneous but limited improvement in gas exchange was seen in the control group, that the protective effect of VCM remained at least for 6 h and that there was no extra benefit on gas exchange by repeating the VCM every hour after CPB. However, before extrapolating these findings to cardiac surgical patients, they should be tested in human controlled studies, with particular attention to the potential harmful effects of VCM.

Acknowledgements

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CASE REPORT

Survival from massive intraoperative pulmonary thromboembolism during orthotopic liver transplantation

M. Manji, J. L. Isaac and J. Bion

Summary

We report a case of massive pulmonary embolism occurring at the time of graft reperfusion in a patient undergoing orthotopic liver transplantation. The clinical diagnosis of pulmonary embolus was aided by on-table echocardiography. Cardiopulmonary bypass and surgical embolectomy prevented her death. We discuss the differential diagnosis, possible aetiology of pulmonary embolism in this context and subsequent management. (*Br. J. Anaesth.* 1998; **80**: 685–687)

Keywords: liver transplantation; monitoring echocardiography, complications pulmonary embolism

Pulmonary embolus is under diagnosed as a cause of death in the perioperative period.[1] Orthotopic liver transplantation (OLT) is associated with acute changes in cardiovascular physiology at the time of reperfusion of the donor liver and these may obscure the diagnosis of pulmonary embolism, with consequent delay in treatment. Anaesthetists need to consider the possibility of acute pulmonary embolism as a cause of severe or prolonged hypotension at reperfusion.

Case report

A 31-yr-old woman with Caroli's syndrome (intrahepatic bile duct dilatation leading to recurrent bile stone formation) was undergoing liver transplantation. All preoperative investigations were normal except for her coagulation profile which was mildly deranged: prothrombin time 16 s (normal 13 s) and partial thromboplastin time 37 s (normal 32 s).

Anaesthesia was induced using standard i.v. induction, followed by neuromuscular block, intubation and ventilation with isoflurane in an air–oxygen mixture. Invasive monitoring included a radial arterial cannula, right internal jugular central cannula and pulmonary artery catheter, derived values from which demonstrated the usual pattern in these patients of increased cardiac output and systemic vasodilatation immediately after induction of anaesthesia (table 1).

Aprotonin was given i.v. throughout the procedure (after a test dose), with an initial loading dose of 2 000 000 u. followed by infusion of 500 000 u. h^{-1}.

After a prolonged dissection (because of the large native liver) veno-venous bypass was established (femoral–portal to axillary) using non-heparin-bonded tubing and a centrifugal pump (Biomedical vortex pump 550, Medtronic). Bypass flow, although continuous, could only be maintained at 1.5 litre min^{-1}, limited by the small size of the axillary vein.

Throughout the anhepatic phase, physiological and coagulation variables remained stable, with coagulation supported by transfusion of fresh frozen plasma. At the end of the anhepatic phase, blood-gas tensions and serum biochemistry were normal.

After blood flushing of the donor liver, declamping of the suprahepatic inferior vena cava (IVC) and portal vein, and reperfusion of the donor liver, there was an anticipated decrease in systemic arterial pressure. This was treated with i.v. volume replacement and increasing doses of norepinephrine, to a maximum of 0.2 $\mu g\ kg^{-1}\ min^{-1}$ to maintain mean arterial pressure at 70–75 mm Hg, with systemic vascular resistance index (SVRI) >1600 dyn s $cm^{-5}\ m^2$. The transplanted liver appeared normal on inspection.

The coagulation profile was within acceptable limits (prothrombin time 22 s, activated thromboplastin time 48 s) and the surgical field showed no signs of oozing. The thrombelastograph tracing at this point suggested a mild hypercoagulable state. In total, she had received 11 u. of fresh frozen plasma.

Approximately 3 min after reperfusion, the liver was lifted to examine the inferior surface for any anastomotic leak. At this point acute haemodynamic changes occurred. Profound systemic hypotension and pulmonary hypertension were accompanied by a broad complex bradycardia on standard CM5 ECG monitoring, in association with a decrease in end-tidal carbon dioxide $P\text{E}'_{CO_2}$, as measured continuously by capnography (4.5 to 0.7 kPa). Airway pressures remained normal. Auscultation of the chest and heart sounds revealed no abnormality. Immediate resuscitation consisted of three doses of epinephrine 1 mg and atropine 3 mg into the central circulation. After a delay of approximately 30–45 s systemic arterial pressure and heart rate responded to the resuscitative measures, but with a marked decrease in cardiac index (CI) (table 1), which could not be improved, even with continuous infusion of high-dose epinephrine.

In an attempt to reduce pulmonary artery pressures, nitric oxide 10 ppm via the inspiratory limb of the ventilator was commenced, together with pulmonary arterial prostacyclin and glyceryl

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Table 1 Cardiovascular variables for the patient during the transplant procedure

	After induction	Anhepatic phase	2 min after reperfusion	5 min after reperfusion	After CPB
MAP (mm Hg)	70	65	75	65	65
CVP (mm Hg)	5	8	10	20	13
CI (litre min^{-1} m^{-2})	4.2	5.0	6.6	1.8	3.5
MPAP (mm Hg)	14	13	19	46	24
SVRI (dyn s cm^{-5} m^2)	1238	912	788	2000	1189
PCWP (mm Hg)	7	9	12	—	14

trinitrate. None of these measures significantly affected pulmonary artery pressures.

The working differential diagnosis was of an excessively severe metabolic response to reperfusion of the donor liver (despite having been routinely blood flushed before reperfusion), air embolus (which seemed unlikely) or massive pulmonary thromboembolism. Reperfusion is usually associated with a period of hypotension, but this generally responds rapidly to i.v. volume, vasoconstrictors and calcium.

At this stage there was evidence of poor tissue perfusion, with anuria and severe metabolic acidosis (pH 7.05, base deficit 15 mEq $litre^{-1}$, lactate 12 mmol $litre^{-1}$). Transthoracic two-dimensional echocardiography was performed with the patient on the operating table and the abdominal incision still open. This revealed good left ventricular function and a dilated right ventricle with right to left deviation of the interventricular septum. Doppler signal showed a waveform suggestive of gross tricuspid regurgitation. No thrombus was seen in the right atrium or ventricle.

The combination of the echocardiographic findings and the clinical picture indicated a diagnosis of massive pulmonary embolism. Hence it was decided to proceed to sternotomy with full cardiopulmonary bypass, and surgical exploration of the main pulmonary trunk.

At sternotomy the right ventricle was seen to be grossly dilated. Cardiopulmonary bypass was instituted immediately and mean perfusion pressure was maintained at 70 mm Hg. Two clots measuring approximately 5×3 cm each were removed from the main pulmonary trunk (fig. 1).

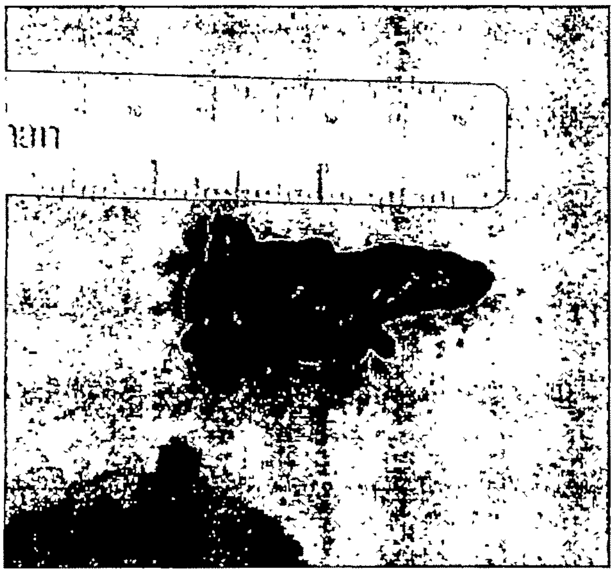

Figure 1 One of the two clots (approximately 5×3 cm) removed from the main pulmonary trunk.

After cardiopulmonary bypass, the right heart remained dilated but performance was much improved. Requirements for epinephrine decreased rapidly and norepinephrine was recommenced with restoration of the usual low SVRI and high CI for this patient population. Recovery of liver perfusion and urine output occurred rapidly.

Her postoperative course in the intensive care unit was complicated by oliguric renal failure and evidence of ischaemic liver injury, but after 6 weeks the patient was discharged to the ward with no neurological impairment and satisfactory renal and liver function. She was discharged home at 8 weeks.

Discussion

There are only two reports in the literature describing acute pulmonary embolism during OLT, both of which were fatal.[2, 3] Echocardiographic studies have shown that pulmonary embolization of air and thrombi is common during graft reperfusion[4] and post-mortem studies have confirmed massive platelet thromboembolism as a cause of sudden death in patients undergoing OLT.[5, 6]

Thrombotic episodes are rarely considered in patients undergoing OLT as coagulopathy is the norm. They have impaired synthesis of clotting factors, are exposed to citrate toxicity, haemodilution and clotting factor consumption, and demonstrate increased fibrinolysis, increased concentrations of tissue plasminogen activator (TPA) and decreased concentrations of TPA-specific inhibitor.[7]

The aetiology of intraoperative pulmonary thromboembolism is multifactorial. In our patient there were several potential contributory factors: first, the large size of the native liver (2485 g) may have caused partial obstruction to the free flow of blood in the IVC; second, fresh frozen plasma may have rendered the patient hypercoagulable during veno-venous bypass, although no clots were seen in the circuit or on the cannulae subsequently; and third, aprotinin together with fresh frozen plasma and a relatively normal prothrombin time may have enhanced the size of an existing clot or even formation of a clot *de novo*. Aprotonin is used during OLT because of its antiplasmin activity and has been described previously as a causative factor in thrombus formation.[3, 8] Finally, an acquired deficiency of antithrombin III, proteins C or S may also accompany liver disease causing a hypercoagulable state.

The appearance of the embolus at embolectomy suggested that the source was from the IVC, perhaps a saddle thrombus, although subsequent venographic examination performed 36 h after operation did not confirm this.

Reperfusion of the donor liver usually causes characteristic changes in cardiovascular physiology, which include pulmonary hypertension in association with severe hypotension, a low SVRI and a high cardiac output.[9] Systemic vasoconstriction is rare and the changes generally respond rapidly to volume expansion. In this case, the correct diagnosis was suggested by systemic vasoconstriction, a low cardiac output, reduced $P\mathrm{E}'_{\mathrm{CO_2}}$ and ECG signs of bundle branch block. The absence of response to pulmonary arterial vasodilators and evidence of acute right heart failure on echocardiography added weight to the diagnosis of massive thromboembolism, and precipitated the subsequent correct management.

The accuracy of echocardiography in the diagnosis of acute pulmonary embolism is uncertain. However, in some clinical situations two-dimensional and Doppler echocardiography may have an important role.[4] In our patient they showed right to left deviation of the interventricular septum, right ventricular dilatation, tricuspid regurgitation and a hyperkinetic left ventricle. The pulmonary trunk was not seen.

The decision to proceed to surgical embolectomy was taken as the patient was deteriorating rapidly and the necessary expert staff and services were on site. While medical therapy with thrombolytic agents is the intervention of choice in uncomplicated massive pulmonary embolism[1] this would have been inappropriate given the ongoing major surgery.

The successful management of massive pulmonary thromboembolism requires a high index of suspicion, supportive clinical findings and readily available cardiothoracic surgical services. Prompt diagnosis is essential, and is made more difficult when the condition occurs in circumstances where it is least expected, and when it mimics expected changes in physiology.

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CITATION CLASSIC

Commentary

Moir DD. Anaesthesia for Caesarean section. *British Journal of Anaesthesia* 1970; **42:** 136–142.

It is interesting to re-read this classic article, and to appreciate how important it was in shaping our views at that time. Although our approach to anaesthesia for Caesarean section has altered fundamentally in the years since this article was written, the changes in the preceding 20 yr had also been dramatic. General anaesthesia was almost universal; during the 1950s, mask anaesthesia was still used widely; during the early 1960s, intubation, in the sitting or left lateral position, was advocated. In 1961, Sellick described cricoid pressure[1] which later came to displace either of these two awkward techniques for avoiding gastric aspiration. Surprisingly, this is not mentioned, and although aortocaval compression was also well described by that time,[2] uterine displacement did not enter routine practice until regional techniques became popular.

This article assesses methods of tracheal anaesthesia that were current and, in advance of its time, compares them with regional anaesthesia. Readers nowadays may be surprised to see the use of: atropine premedication, then an accepted routine; the rather long-acting neuromuscular blocking agent tubocurarine; and lidocaine for regional anaesthesia. Bupivacaine, a more suitable agent, did not come into general use until this work was well under way.

The article describes two studies, one of maternal blood loss, arterial pressure and awareness, and the other of neonatal welfare, the latter recruiting only normal elective cases. There is some uncertainty about the numbers of patients studied. The author claims only 265, but if there is no overlap among the women in the two studies, as is implied, the total is 295. (What were the referees, editor and sub-editor doing?) Whether the total is 265 or 295, this represents a formidable amount of work for a single author.

The study of blood loss is admirable. The washing machine method, the gold standard for obstetrics, was used. The finding that blood loss was significantly reduced in the group receiving regional anaesthesia, and that this was not, apparently, related to relative hypotension in the regional anaesthesia group, is fundamental. That by current standards a rather low volume of local anaesthetic was used, with no mention of whether patients were comfortable during surgery or how many required supplementation, is probably immaterial. Today, however, hypotension would require a stricter definition.

Awareness was reported by only two women, one of whom recalled intubation, which would be attributable to an inadequate dose of thiopental rather than inadequate maintenance. Detection of awareness, however, depended only on voluntary reporting by patients. In those days, mothers were less inclined to complain than they are today, and therefore I question if this is a sufficiently sensitive method. Moreover, Tunstall had not yet described his epoch-making isolated forearm technique[3] which revealed that amnesic wakefulness can occur in the absence of recall. Nevertheless, this study was instrumental in pointing out the need for supplementation of nitrous oxide.

Dr Moir also demonstrated significantly higher Apgar scores with 50% nitrous oxide and halothane compared with 70% nitrous oxide alone (chi-square=21, although this was not mentioned), attributing this to increased $F_{I_{O_2}}$. Nowadays, a single estimate of Apgar score would not usually be sufficient to detect differences in neonatal well-being between treatment groups following elective Caesarean section, and funic acid–base status and neurological and adaptive capacity scores are required. In some cases "aspiration of liquor amnii" was blamed. This is unlikely to mean *meconium* aspiration unless these previously low-risk babies were rendered hypoxic; babies normally breathe amniotic fluid in utero. Aortocaval compression as well as hypoxia may have contributed to the relatively poor outcome of some babies.

It has been regrettably common, from that day to this, to fear anaesthetizing the baby. This is an entirely inappropriate concern. Anaesthesia is normally too brief to have significant fetal effects and is an innocuous and reversible process, whereas maternal stress caused by inadequate anaesthesia is a potential cause of fetal hypoxia, a far more damaging situation. However, it is preferable for the baby to give the mother adequate anaesthesia than sedative premedication, as mooted by Dr Moir, as the latter may cause more prolonged neonatal depression. Babies clearly benefit from good maternal oxygenation, but nowadays the appropriate concentration of oxygen for each individual mother can be determined with the aid of pulse oximetry. The factor that limits the concentration of volatile anaesthetic is not the baby but post-partum uterine relaxation, so between the devil and the deep blue sea most anaesthetists select regional anaesthesia, thereby also avoiding airway problems, hence the current increase in popularity of subarachnoid block.

Readers will note no mention of difficult intubation, gastric aspiration or antacid premedication. Death from aspiration of gastric contents was at its peak between 1964 and 1970; perhaps the author wisely eschewed the dangerous but then fashionable practice of ladling particulate antacids into all parturients.

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ANAESTHESIA FOR CAESAREAN SECTION

An Evaluation of a Method using Low Concentrations of Halothane and 50 per cent of Oxygen

BY

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SUMMARY

The addition of 0.5 per cent of halothane vapour to a basic thiopentone, nitrous oxide, muscle relaxant anaesthetic technique does not increase blood loss at Caesarean section, does not affect the incidence of hypotension, and is likely to ensure unconsciousness. By permitting the administration of 50 per cent of oxygen with nitrous oxide, the condition of the newborn infant is likely to be improved. The use of 0.8 per cent of halothane vapour does not increase blood loss but is associated with a high incidence of hypotension and for this reason is not advisable.

Following upon the work of Hodges and his colleagues (1959), Hodges and Tunstall (1961) and Crawford (1962) a thiopentone, nitrous oxide muscle relaxant technique of anaesthesia with intermittent positive pressure ventilation (IPPV) has been generally used, at least in the United Kingdom, for anaesthesia for Caesarean section. This technique is deservedly popular because in skilled hands it comes close to solving many of the problems of obstetrical anaesthesia.

Some problems remain and there has been a disturbing increase in the number of deaths due to obstetric anaesthesia (Report on Confidential Enquiries, 1964–66). The blood loss at Caesarean section under general anaesthesia with nitrous oxide and muscle relaxants averages almost 1000 ml (Brant, 1966; Wallace, 1967) and the blood loss at forceps delivery under the same type of anaesthesia averages over 500 ml (Moir and Wallace, 1967). About 2 per cent of patients are likely to be awake during Caesarean section (Crawford, 1962; Hartridge and Wilson, 1963; Wilson and Turner, 1969).

Finally there is the question of the percentage of oxygen in the inspired gas mixture which will produce optimal foetal oxygenation. Rorke, Davey and Dutoit (1968) in a study of patients undergoing elective Caesarean section found that foetal oxygenation and neonatal Apgar scores were maximal when approximately 66 per cent of oxygen was administered to the mothers. This percentage was superior to either 33 per cent or 100 per cent of oxygen. If low percentages of nitrous oxide are to be used, then supplementary anaesthesia will often be necessary to ensure unconsciousness in the mother.

It was therefore decided to assess the influence of unsupplemented 70 per cent nitrous oxide in oxygen on blood loss, blood pressure, awareness and the Apgar score of the newborn infant at Caesarean section and to compare the finding with those obtained when a 50:50 mixture of nitrous oxide and oxygen was used with supplementary low concentrations of halothane. Blood losses were also measured in a small series of Caesarean sections performed under lumbar epidural analgesia.

METHOD

Two hundred and sixty-five patients were studied in two groups. The first group, in which the influence of anaesthesia on blood loss and blood pressure was assessed, consisted of 145 unselected patients undergoing Caesarean section and anaesthetized by one of four anaesthetic techniques. The second group was composed of 150 patients who had elective Caesarean section performed under one of two general anaesthetic techniques.

General anaesthesia was administered to 245 patients and 20 patients received only lumbar epidural analgesia. Random allocation to a particular anaesthetic technique was practised, except

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in the case of the small group who had epidural analgesia. The only exclusions from the first group, where blood loss measurements were made, were patients with antepartum haemorrhage or multiple pregnancy. There were therefore elective and emergency operations and a wide variety of indications for Caesarean section in this group. The second group of 150 elective Caesarean sections, in which the Apgar score system was used to compare the effects of unsupplemented 70:30 nitrous oxide and oxygen with 50:50 nitrous oxide and oxygen and 0.5 per cent of halothane, was a carefully selected group. The patients were not in labour, did not have pre-eclampsia, placental insufficiency, diabetes mellitus or rhesus incompatibility. The period of gestation was between 37 and 41 weeks and there were no multiple births.

Anaesthetic techniques.

A basic technique was used for each of the 245 patients who received general anaesthesia. The only variations were the use of either 30 per cent or 50 per cent oxygen with nitrous oxide and the addition of either 0.5 per cent or 0.8 per cent of halothane vapour when 50 per cent of oxygen was administered.

No sedative or analgesic premedication was given, although most patients who were in labour had received drugs of this type earlier in labour. Atropine 0.6 or 1.2 mg was injected intravenously just before induction of anaesthesia. After pre-oxygenation for 2 minutes, thiopentone 200 or 250 mg was injected and the trachea was intubated after the administration of suxamethonium. Relaxation was maintained with tubocurarine and IPPV was performed by a mechanical ventilator using a non-rebreathing circuit and an expired minute volume of 7–8 l./min. Halothane, if used, was administered from a Halox vaporizer. The fresh gas flow just exceeded the patient's minute volume. In these circumstances, the precise dose of halothane taken up by the patient is not known.

Ergometrine 0.5 mg was given intravenously at delivery of the child and each patient received 1000 ml of Ringer's lactate solution intravenously during the operation. Blood was transfused at the discretion of the anaesthetist. Blood pressures were recorded by sphygmomanometer at 5-minute intervals.

The interval between the induction of anaesthesia and the delivery of the child was from 12 to 22 minutes.

Lumbar epidural analgesia was administered by a single-shot or a catheter technique to 20 patients for emergency and elective Caesarean section. From 12 to 14 ml of a 2 per cent lignocaine solution with 1:200,000 adrenaline added, were injected at the L2–3 or L3–4 interspace. No premedicant drugs were given. These patients were fully conscious and breathed air. No vasopressor drugs were used.

Blood loss measurements.

A haemoglobin extraction-dilution method (Thornton et al., 1963) was used to measure blood loss at 145 Caesarean sections. All blood, blood-stained linen and swabs were put into a Rustad-Ohlin Perdometer (Rustad, 1963) and washed. The haemoglobin content of the known volume of wash water was measured and the blood loss calculated semi-automatically by the apparatus. This method is particularly suited to obstetrics and its details and accuracy in suitable circumstances have been described previously (Wallace, 1967; Moir and Wallace, 1967; Bond, 1969). The accuracy of the apparatus was assessed by measuring known volumes of expired bank blood from time to time. The recovery rate was always at least 98 per cent.

Awareness during anaesthesia.

For the purpose of this study, only a definite recollection of specific events, painful or otherwise, during the period of surgery was recorded as awareness. It is possible that earlier or closer questioning deliberately directed towards eliciting recall of awareness and phenomena such as unpleasant dreams might have evoked a higher number of positive responses than was actually obtained (Wilson and Turner, 1969). Leading questions were not asked and positive recall was often first mentioned by the patient to the nursing staff.

Condition of the newborn.

Because of the wide variety of indications for Caesarean section in the first group of patients and the consequent lack of validity of any comparison of the status of the infants, a separate series of 150 elective Caesarean sections was used to make a more valid assessment, based on the Apgar scoring system. The obstetric conditions which were excluded from this series have been listed and no patient with an existing condition which might have predisposed to foetal or neonatal hypoxia was included in this group.

Unsupplemented nitrous oxide with 30 per cent of oxygen was given to 75 patients and 75 patients received a 50:50 nitrous oxide and oxygen mixture to which 0.5 per cent of halothane vapour had been added. Patients were allocated at random to one of these two anaesthetic techniques.

The Apgar score of each infant was assessed independently by a paediatrician, 2 minutes after delivery. The paediatrician was unaware of the anaesthetic used. All infants received facial oxygen and pharyngeal suction, usually under direct vision with a laryngoscope. Further resuscitative measures were performed, where necessary, at the discretion of the paediatrician.

RESULTS

Blood loss.

The mean blood losses, with standard deviations, are shown in table I, according to the anaesthetics used at 145 Caesarean sections. The mean blood loss with epidural analgesia is approximately half that associated with any of the general anaesthetics. The Student *t* test shows that this difference is highly significant in each case ($P<0.01$).

The difference between the mean blood losses associated with each of the three general anaesthetics is not great and is not statistically significant ($P<0.2$–0.4).

It is concluded that epidural analgesia substantially reduces bleeding at Caesarean section in comparison with the general anaesthetics assessed. It is also concluded that the addition of up to 0.8 per cent of halothane vapour to nitrous oxide and oxygen anaesthesia has no significant effect on bleeding.

Table II shows the numbers of patients who lost more than 1 litre of blood at Caesarean section. It is noteworthy that no patient in the small series of epidural blocks lost as much as a litre of blood and that, in this respect, the worst anaesthetic was actually the unsupplemented 70:30 nitrous oxide and oxygen technique.

TABLE I

The influence of anaesthesia on blood loss at 145 Caesarean sections.

	Anaesthetic			
	N_2O/O_2 (70:30) 50 cases	N_2O/O_2 (50:50) +0.5% halothane 50 cases	N_2O/O_2 (50:50) +0.8% halothane 25 cases	Epidural analgesia 20 cases
Loss (ml) mean ± SD	792 ± 388	688 ± 206	702 ± 294	378 ± 146

TABLE II

Numbers of patients losing over 1 litre of blood at 145 Caesarean sections.

	Anaesthetic			
	N_2O/O_2 (70:30) 50 cases	N_2O/O_2 (50:50) +0.5% halothane 50 cases	N_2O/O_2 (50:50) +0.8% halothane 25 cases	Epidural analgesia 20 cases
Number losing over 1 litre	15 (30%)	6 (12%)	4 (16%)	None

TABLE III

The influence of anaesthesia on hypotension (<90 mm Hg) at 145 Caesarean sections.

	Anaesthetic			
	N_2O/O_2 (70:30) 50 cases	N_2O/O_2 (50:50) +0.5% halothane 50 cases	N_2O/O_2 (50:50) +0.8% halothane 25 cases	Epidural analgesia 20 cases
Number of patients with hypotension	2 (4%)	2 (4%)	7 (28%)	2 (10%)

Hypotension.

The numbers of patients whose systolic blood pressures fell to 90 mm Hg or lower, before delivery of the foetus, is shown in table III. The high incidence of hypotension with 0.8 per cent of halothane caused this technique to be abandoned when 25 patients had been anaesthetized in this way. The incidence of hypotension (below 90 mm Hg) was the same (4 per cent) when unsupplemented nitrous oxide and 50:50 nitrous oxide and oxygen with 0.5 per cent of halothane were used. It is likely that compression of the inferior vena cava by the uterus and vasodilatation due to the effects of anaesthesia combined to produce hypotension.

Awareness during anaesthesia.

Two of the 50 patients anaesthetized with unsupplemented nitrous oxide and oxygen (70:30) had clear recall of events which occurred during anaesthesia. One of these patients remembered what was probably intubation of the trachea and the other remembered the delivery of her child, having experienced pain at that time, and she also had a clear memory of a conversation which took place in theatre. None of the patients who received halothane in addition to 50:50 nitrous oxide and oxygen volunteered any recollection of awareness during anaesthesia, although one patient had blinked and moved her head under 0.5 per cent halothane anaesthesia.

The numbers of patients in the series under consideration is small. However, since completing the investigations which are the subject of this communication, a further 120 patients have been anaesthetized for Caesarean section with 50:50 nitrous oxide and oxygen and 0.5 per cent of halothane. Thus, in a total of 245 patients anaesthetized with this technique, no patient has had any recall of events during anaesthesia.

Condition of the newborn infant.

Table IV shows the 2-minute Apgar scores of the separate series of infants delivered by elective Caesarean section from mothers who had no apparent obstetric condition predisposing to foetal or neonatal hypoxia. Unsupplemented nitrous oxide and oxygen (70:30) was given to 75 mothers and the other 75 patients received nitrous oxide and oxygen (50:50) with 0.5 per cent of halothane.

All babies were born alive and there were no neonatal deaths. The incidence of low Apgar scores was greater when unsupplemented 70:30 nitrous oxide and oxygen was used, and the incidence of high Apgar scores was substantially lower with this technique.

TABLE IV

The influence of anaesthesia on the Apgar scores at 150 elective Caesarean sections.

Apgar score (at 2 minutes)	N_2O/O_2 (70:30) 75 cases	N_2O/O_2 (50:50) +0.5% halothane 75 cases
8–10	41 (55%)	67 (89%)
4–7	26 (35%)	6 (8%)
1–3	8 (10%)	2 (3%)

Apgar scores of 3 or under were attributed on three occasions to the aspiration of liquor amnii. There is no readily apparent explanation for the other seven Apgar scores of 3 or under.

It appears that more infants are likely to be born in good condition and that fewer are likely to be born in poor condition when a 50:50 nitrous oxide and oxygen mixture, supplemented with 0.5 per cent halothane, is used than when only 30 per cent of oxygen is administered. There is no suggestion that 0.5 per cent of halothane causes neonatal respiratory depression but rather that by permitting the administration of 50 per cent of oxygen to the mother, while yet ensuring unconsciousness, the condition of the newborn is likely to be improved.

DISCUSSION

The few published figures of blood loss at Caesarean section using an accurate method of measurement indicate that the average blood loss is about 1 litre and that the range of values is wide (Brant, 1966; Wallace, 1967). The influence of anaesthesia on blood loss does not appear to have been accurately assessed.

A haemoglobin extraction-dilution technique was used to measure blood loss in the present series. Potential sources of error in this method have recently been discussed, but when carefully performed it is sufficiently accurate for clinical purposes (Bond, 1969) and for an investigation such as the present one. Assuming reasonable care in measuring volumes of water and patient's haemoglobin values, a source of error may lie in failure to allow for the effect of anaesthesia on haemoglobin value and for changing haemoglobin values during bleeding. The drop in haemoglobin level associated with anaesthesia itself averages about 3 per cent (Bond, 1969) while at Caesarean section most of the bleeding occurs rapidly after delivery of the child so that compensatory haemodilution is unlikely to influence results to an important degree.

Haemoglobin extraction-dilution methods remain the most suitable way of estimating external blood loss in obstetrics, because they allow estimations of all blood shed into bottles and on to drapes, swabs, clothing and the floor. Contamination with liquor amnii, urine and antiseptics does not influence the result (Moir and Wallace, 1967).

The accuracy of the Rustad-Ohlin Perdometer itself was found to be over 98 per cent at several checks during this study.

This was an unselected series of Caesarean sections and it is possible that obstetric variables may have influenced blood loss. However, some factors including parity, the elective or emergency nature of the operation, and whether it is a first or subsequent Caesarean section, have been found not to influence blood loss significantly (Brant, 1966; Wallace, 1967). Patients with antepartum haemorrhage and twin pregnancy were excluded from the present series. In a study of the influence of anaesthesia on blood loss at forceps delivery it was found that the only obstetric factor which significantly affected blood loss was inco-ordinate uterine action in the first stage of labour (Moir and Wallace, 1967). In this series of forceps deliveries, epidural analgesia approximately halved the blood loss in comparison with general anaesthesia, an effect which was also observed in the present series of Caesarean sections.

There is no evidence that the use of halothane in concentrations of either 0.5 per cent or 0.8 per cent with nitrous oxide and oxygen in a non-rebreathing circuit causes increased bleeding at Caesarean section in comparison with unsupplemented nitrous oxide and oxgen. Indeed there was actually less bleeding where halothane was in use, although the difference was not statistically significant.

Many anaesthetists subscribe to the view of Crawford (1965) that halothane has little place in obstetric anaesthesia because of its myometrial relaxant property. Yet halothane has been used in obstetric anaesthesia on both sides of the Atlantic (Dixon and Matheson, 1958; Allard and Guimond, 1964; Stoelting, 1964; Johnstone and Breen, 1966; Batt, 1969). These writers have all thought that halothane did not increase bleeding at various obstetric operations, including Caesarean section, provided that it was used in minimal narcotic concentrations. It should be noted that some of these workers used halothane to produce only transient, light narcosis and all seem to have relied on imprecise methods of blood loss estimation.

Halothane undoubtedly can depress myometrial contractility (Vasicka and Kretchmer, 1961). The in vitro finding of Munson and his colleagues (1969) indicates that the contractibility of isolated human myometrium is not inhibited until the level of halothane reaches the equivalent of an inspired concentration of 1.2 per cent. Klide, Penna and Aviado (1969) found that concentrations of halothane of 1 to 2 per cent depressed the contractions of isolated rabbit myometrium and that this inhibition could be reversed by beta-adrenergic blocking drugs.

Higher concentrations of halothane are certainly dangerous in obstetric anaesthesia, but it would appear from clinical experience, in vitro studies and from measurements of blood loss that halothane can be administered in concentrations of up to about 1 per cent without producing uterine relaxation of practical significance.

The incidence of hypotension to below 90 mm Hg systolic was the same (4 per cent) with the basic nitrous oxide technique and the 0.5 per cent halothane technique. When 0.8 per cent of halothane was used the incidence of hypotension rose to an unacceptable level of 28 per cent and led to the early abandonment of this technique, especially as no advantage accrued from the use of more than 0.5 per cent of halothane.

Having established the possibility of administering 0.5 per cent of halothane with a 50:50 nitrous oxide and oxygen mixture without increasing bleeding or the incidence of hypotension at Caesarean section, the possible merits of such a technique over the basic 70:30 nitrous oxide and oxygen mixture must now be considered. Potential advantages might be the abolition of awareness during anaesthesia and an improvement in the condition of the newborn infant.

At present 245 patients have been anaesthetized for Caesarean section when anaesthesia was maintained with a 50:50 nitrous oxide and oxygen mixture with the addition of 0.5 per cent of halothane vapour and none of these patients has had any factual recall of events during anaesthesia. Others have reported factual recall in about 2 per cent of patients anaesthetized for Caesarean section with unsupplemented nitrous oxide and oxygen and a 17 per cent incidence of some unpleasant or painful memory (Wilson and Turner, 1969). In the writer's hospital 13 of 1216 patients anaesthetized for Caesarean section with unsupplemented 70 per cent of nitrous oxide have had clear recall of events during anaesthesia.

There is, in this writer's opinion, good reason for the supplementation of nitrous oxide anaesthesia in order to diminish or abolish the possibility of awareness, provided that no additional hazards are introduced for mother or child. An alternative approach to this problem is the use of sedative premedication. The use of a volatile supplement to nitrous oxide anaesthesia has the inherent advantage that should neonatal respiratory depression develop, elimination of the volatile agent by the lungs is easily achieved, whereas elimination of injected sedative or analgesic drugs is slow.

In the series of 150 elective Caesarean sections, selected for the absence of any pre-existing cause for foetal hypoxia, the conditions of the infants, as judged by the 2-minute Apgar scores, was substantially better when the mothers had received the 50:50 nitrous oxide and oxygen mixture with 0.5 per cent of halothane. The explanation for this is probably to be found in the work of Rorke, Davey and Dutoit (1968) which stimulated the present study. These workers found that, as the maternal Pa_{O_2} rose towards 300 mm Hg, foetal oxygenation and neonatal Apgar scores improved. There was a slight decrease in umbilical venous and arterial oxygen tensions when the material Pa_{O_2} rose above the optimal value of 300 mm Hg. In this investigation the influence of many obstetric and anaesthetic variables was minimized or eliminated. Unfortunately Rorke, Davey and Dutoit used more than one volatile anaesthetic supplement and it is not therefore certain that the observed effects on foetal oxygenation were attributable solely to the variations in maternal Pa_{O_2}. Vasoconstriction in the placental vasculature in response to high oxygen tensions is suggested as the explanation for the failure of an increase in Pa_{O_2} to above 300 mm Hg to increase foetal oxygenation. Breathing 50 per cent of oxygen should produce a maternal Pa_{O_2} closer to the optimal 300 mm Hg than the standard 30 per cent of oxygen.

Although 0.5 per cent of halothane has been found to be a safe and effective supplement to a 50:50 nitrous oxide and oxygen mixture for the maintenance of anaesthesia during Caesarean section, it is likely that other anaesthetic agents could be equally satisfactory in comparable minimal concentrations. The effects of anaesthetic agents on the uteroplacental circulation might be relevant in the choosing of a supplement to 50:50 nitrous oxide and oxygen, but these effects do not appear to have been studied.

A disconcerting finding was that a few infants had low Apgar scores with both anaesthetics used for the elective Caesarean sections, although the number was greater with the unsupplemented 70:30 nitrous oxide and oxygen anaesthesia. In three infants, the cause was aspiration of liquor amnii at birth. There was no obvious explanation for the poor condition of the other seven infants who had Apgar scores of 3 or less at 2 minutes. Aspiration of liquor amnii is a recognized risk at elective Caesarean section and undetected aspiration may have occurred in other infants. Extreme maternal hyperventilation causes neonatal depression (Morishima et al., 1963; Moya et al., 1965) but it is unlikely that this degree of respiratory alkalosis developed in the conditions of the present investigation where the maternal minute volume did not exceed 8 l./min. There was no association between maternal hypotension and low Apgar scores.

The use of the 2-minute Apgar scores for neonatal assessment is open to some criticism. Infants with low 2-minute scores may be in good condition by 5 minutes of age and the Apgar score at any age gives equal emphasis to relatively unimportant features such as skin colour and to vital signs such as heart rate and respiratory activity. The method is in general use and is in routine use, at 2 minutes of age, in the Queen Mother's Hospital. Because the assessments were made as part of the normal routine by the paediatricians who had no knowledge of the anaesthetic in use, there can be no question of bias in the allocation of Apgar scores.

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L'ANESTHESIE DANS LES CESARIENNES: EVALUATION D'UNE METHODE UTILISANT DE L'HALOTHANE A FAIBLES CONCENTRATIONS ET 50 POUR CENT D'OXYGENE

SOMMAIRE

L'adjonction de 0,5 pour cent de vapeurs d'halothane à du thiopentone base, oxyde nitreux, constitue une technique anesthésique de relâchement musculaire qui n'augmente pas la quantité des pertes sanguines au cours de la césarienne, n'influence pas l'apparition d'une hypotension et provoque vraisemblablement une inconscience. L'administration de 50 pour cent d'oxygene avec l'oxyde nitreux permet trés probablement d'améliorer la condition du nouveau-né. L'utilisation de 0,8 pour cent de vapeurs d'halothane, n'augmente pas le volume de la perte sanguine mais provoque fréquemment une hypotension et n'est donc pas conseillée pour cette raison.

NARKOSE BEIM KAISERSCHNITT: BEWERTUNG EINER NARKOSETECHNIK MIT NIEDRIGER HALOTHAN-KONZENTRATION UND 50 PROZENT SAUERSTOFF

ZUSAMMENFASSUNG

Zugabe von 0,5 Prozent Halothandampf zu einer Basisnarkose mit Thiopentone, Lachgas und Muskelrelaxantien verursacht keinen erhöhten Blutverlust bei der Sectio Caesarea. Sie ändert nicht die Häufigkeit des Blutdruckabfalls. Sie ist geeignet, Bewußtlosigkeit zu gewährleisten. Das Befinden der Neugeborenen wird gewöhnlich verbessert, wenn man mit Lachgas 50 Prozent Sauerstoff zuführt. Auch die Verwendung von 0,8 Prozent Halothan verursacht keinen erhöhten Blutverlust, jedoch ist eine solche Konzentration wegen des häufigen Vorkommens von Blutdruckabfall nicht zu empfehlen.

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CORRESPONDENCE

Nitric oxide (NO)/nitrogen dioxide (NO_2) scavengers

Editor,—After reading with interest the study by Weimann and colleagues[1] on a subject that we have recently reviewed,[2] we would like to make the following comments.

We were surprised by the hypothesis of improved NO_2 absorption through increasing the potassium hydroxide (KOH) content of soda lime, because Pickett and colleagues[3] found a marked reduction in NO_2 concentration (80.6% or 100%, depending on the electrochemical monitor used) and to a lesser extent in NO concentration (13.3% or 8.2%) using ethyl violet Intersorb™ soda lime without KOH. Moreover, Ishibe and colleagues[4] found similar absorption properties for two types of soda lime (100% for NO_2, from 11.9% to 97.1 % for NO with Soda Sorb™, and from 20.6% to 90.1 % for NO with Wako lime-A™, depending on the respective concentrations of NO and NO_2 passing through the absorber). The absorbers had the same indicator agent (ethyl violet) but with one major variation in chemical composition—the presence of 5% KOH in Soda Sorb™. It was stated that NO_2 is mainly absorbed by chemical neutralization with ethyl violet soda lime, but NO is absorbed with equimolecular amounts of NO_2 only where they coexist.[2 4 5] For this reason, it would have been interesting if the authors had presented the different rates of NO_2 production for the three concentrations of NO (20, 40, and 80 ppm) and fractions of inspired oxygen (0.25, 0.75, and 0.99) used, as well as the different levels of NO and NO_2 absorptions under these such conditions. This would explain the levels of NO absorption observed for Drägersorb 800™ (2%) and Sofnolime™ (3%). 2 ppm of NO_2/80 ppm of NO = 2.5% absorption for NO.

Moreover, the authors mentioned the concentration of NO (1000 ppm) in the gas cylinder but not that of NO_2. This is important because it was previously indicated[6] that a cylinder of 993 ppm NO contained as much as 17 ppm of NO_2 (in our case, 900 ppm NO cylinders contain less than 5 ppm of NO_2[7]). Weimann and colleagues reported a maximum concentration of 2 ppm NO_2 measured in the extreme conditions of testing.[1]

Until now only two abstracts[8 9] have reported partial absorption of NO_2 using ethyl violet soda lime, while other reports (reviewed in Francœur *et al*[2]) indicated almost full absorption. The apparent discrepancy may be explained by technical reasons, as suggested by Weimann.[1] In particular, we noted a difference in the chemical composition of the soda lime preparations with a higher content of calcium (around 75%) and sodium (around 3%) hydroxides.[3–5] Weimann and colleagues suggest a ceiling effect in NO_2 absorption with increased KOH content: there was no difference between Special-1 (3.0% KOH) and Special-2 (7.3% KOH) in NO_2 absorption (respectively, 47% and 46%). We think that this ceiling effect would reveal a lack of correlation between the content of KOH and the level of NO_2 absorption. From all these results, it would appear that the primary determinant of NO_2 absorption is the content of calcium hydroxide, and that KOH has only a limited role.

We also noted major mistakes in the references cited in the discussion.[1] First, Stenqvist and colleagues[10] did not report a NO_2 absorption "by almost 80%",[1] but between 87.5% and 100%. Second, we have reported above the exact levels of NO absorption found in the study by Ishibe and colleagues.[4] Third, the paper by Pickett and colleagues,[3] presented in Weimann's discussion, is not a good reference. The one cited refers to a first series of experiment by Pickett and colleagues,[11] which was subsequently corrected with technical modifications.[3]

As outlined by the authors,[1] other materials such as molecular sieve 5A™,[12] ABEK HgCONO-P3™,[13] or charcoal[14] have been found efficient for NO and NO_2 adsorption and useful for environmental protection. Moreover, Vaahs and colleagues[15] showed that the noXon™ polymeric filter completely and selectively removes all NO_2 from the inspiratory gas. The advent of new, efficient and selective filters such as noXon™, added to the reliability in delivering precise and constant concentrations of the new NO delivery devices—such as I-NOvent™ (Ohmeda, Liberty Corner, New Jersey, USA), NOdomo™ (Dräger, Lübeck, Germany), NAMU™ (Messer-Griesheim/Nellcor Puritan Bennett Canada, Kirkland, Canada), Servo Ventilator 300™ with NO option (Siemens-Elema, Solna, Sweden), etc—raises questions over the need for continuous monitoring of inspired NO_2 concentrations. A regular check might be sufficient.

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Editor,—Thank you for giving us the opportunity to comment. In their letter, Drs Troncy, Francœur, and Blaise question the need for continuous monitoring of inspired NO_2 concentrations during inhaled NO treatment and state that instead "a regular check" may be sufficient. We strongly disagree with this statement.

Nitric oxide inhalation treatment is not yet approved for clinical use and has still to be treated as an investigational drug. Therefore all possible measures should be undertaken to minimize harm to patients treated with this drug—as stated in the Declaration of Helsinki. This requirement has led to the development of safety guidelines for the clinical use of inhaled NO that include the continuous measurement of NO and NO_2.[1 2] This capability is also included in the standards proposed by the American Food and Drug Administration (FDA) for NO and NO_2 monitoring devices.[3] Several studies[4 5] showed that current NO delivery devices are not as accurate as suggested by Troncy and colleagues. This is important since the conversion rate of NO to NO_2 is determined by the square of the NO concentration, the O_2 concentration, and the residence time of NO with O_2,[4] where the latter is a result of the chosen mechanical ventilator setting. The frequent changing of settings of these variables—essential during treatment of the critically ill patients who require NO treatment—and the possible inaccuracy of NO delivery may lead to rapid and unpredictable changes in NO_2 concentration, which should therefore be monitored continuously. Accordingly, all the NO delivery devices mentioned by Troncy are capable of continuous NO and NO_2 monitoring. Nevertheless, not all of these devices are available in or meet the medical safety regulations of all countries.

There is clear evidence that NO_2 inhalation may be toxic to the lung, even in the concentrations that may occur during clinical NO administration[7] (for review see our original report[8]). Furthermore, Troncy and colleagues point out that NO cylinders may be contaminated by large amounts of NO_2—that is, 17 ppm NO_2 (Tibbals and colleagues[9]) or 12 ppm NO_2 (Stenqvist and colleagues[10]). Such contamination may be harmful if not recognized by inspired NO_2 monitoring.[11]

Besides our report[8] and the two abstracts cited by Dr Troncy, two other publications showed only partial absorption of NO_2 by soda lime[10 12]: Stenqvist and colleagues[10] used Q-Sorb™ which contains ethyl violet and stated that "the NO_2 concentration was reduced by about 75%"—which we referred to as "almost 80%".[8] Westfelt and colleagues[12] also reported NO_2 absorption of only 65–70% using the same soda lime preparation (Q-Sorb™). Only partial NO_2 absorption by soda lime and the possibility of new NO_2 formation in the inspiratory limb between the soda lime absorber and the Y-piece emphasize the need to monitor NO_2 at the inspiratory side of the Y-piece. Our data did not reveal any correlation between the NO_2 concentration and the NO extraction rate, as proposed by Ishibe and colleagues.[13]

The study by Stenqvist and colleagues[10] has been cited correctly (see above). We would like to thank Dr Troncy for clarifying the actual values for NO absorption found by Ishibe and colleagues.[13] The values cited from Pickett and colleagues are, in fact, derived from their later study,[14] which we did not state in our paper.

Our data suggest that NO_2 absorption by soda lime may be correlated with the potassium hydroxide (KOH) content of the soda lime preparation: the higher the KOH content the more NO_2 is absorbed. The effect of KOH content on NO_2 absorption may already be maximal at 3.0%, which would explain the fact that Special-2 soda lime was not shown to absorb more than Special-1. We showed clear differences between the five studied soda lime preparations but there was no significant difference in their calcium hydroxide content. Therefore, our data do not support the conclusion by Dr Troncy that the content of calcium hydroxide is the primary determinant for NO_2 absorption by soda lime.

We note that Dr Troncy and colleagues agree with us that different technical approaches for examining a certain scientific question may lead to different results. In our original report[8] we discussed in detail the technical differences that may be responsible for the different results of the studies of Pickett and colleagues,[15] Ishibe and colleagues,[13] Stenqvist and colleagues,[10] and our own.[8] In contrast to the studies by Pickett and colleagues[15] and Ishibe and colleagues,[13] our set up was specifically designed to mimic the clinical situation as closely as possible. Further investigations may be required to elucidate the exact mechanisms by which NO and NO_2 absorption by soda lime occurs and how it may be improved. However, current published reports agree that certain soda lime preparations can absorb NO_2 and therefore may be useful in reducing the risk of potentially harmful side effects and in increasing the safety of NO inhalation treatment.

Meanwhile, the use of inhaled nitric oxide therapy should carefully follow the recent recommendations of an expert panel, which include that "NO and NO_2 should be monitored continuously at the inspiratory side of the Y-piece .. ".[1]

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Transposition of rotameter tubes

Editor,—Walmsley and Holloway are right to highlight the need for comprehensive checking.[1] Considering the Association of Anaesthetists' 1990 checklist[2] unsuitable for daily pre-use checks, COVERS[3] was introduced in this hospital as a pre-use checklist broadly equivalent to the subsequently introduced 1997 Association revision.[4] Also recognising the need for a formal schedule of comprehensive checking, COVERS is backed up by the performance of an extended checklist based on the 1990 recommendations which is carried out by anaesthetist and operating department assistant together before use, whenever a machine is returned from service or breakdown, and also midway between scheduled services.

Our audit[5] confirmed the benefits of this routine. The combination is appropriate for the delivery of safe anaesthesia and the management of risk within the directorate.

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1. Walmsley AJ, Holloway J. Transposition of rotameter tubes. *British Journal of Anaesthesia* 1998; 80: 124–5.
2. The Association of Anaesthetists of Great Britain and Ireland. *Checklist for anaesthetic machines; a recommended procedure based on the use of an oxygen analyser.* London: AAGBI, 1990.
3. Krimmer M, Lake APJ, Wray I. COVERS for anaesthetic machines: an audit and standard. *European Journal of Anaesthesiology* 1997; 14: 505–13.
4. The Association of Anaesthetists of Great Britain and Ireland. *Checklist for anaesthetic apparatus 2.* London: AAGBI, 1997.

Editor,—Thank you for giving me the opportunity to reply to Dr Lake's comments about our letter.

The COVERS comprehensive check list described by Krimmer and colleagues for use on machines after a service deals with some of the points we suggested in our letter. However, even this checklist—although it states that the flow through the oxygen and nitrous oxide flowmeters should be set at 5 litres/min, and not approximately 5 litres/min as suggested by the Association of Anaesthetists of Great Britain and Ireland check list—would not necessarily prevent a switch of flowmeters. Although the COVERS check list is extremely thorough, perhaps we could suggest adding a further point to the checklist by making sure that the flowmeter is labelled appropriately above each flow control valve. Perhaps also, as suggested in our letter, the flowmeters should be designed so that they could not be interchanged.

In summary, although COVERS is a more thorough and comprehensive checking system than the AAGBI guidelines, particularly after anaesthetic machine servicing, we are still not convinced that it would necessarily always pick up problems such as flowmeter transpositions similar to the one described in our letter.

A J Walmsley
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Editor,—I write regarding the letter from A J Walmsley concerning transposition of rotameter tubes.[1] ISO 5358 1980 para 11.8 states that "the manufacturer shall, as far as practicable, ensure that the flow meters and their tubes are not interchangeable between correct flow meter locations or between high and low flow locations of the same gas." Other standards, such as BS 4272, part 3, 1989, JIS T 7201, 1990, and ASTM F1161, 1988, all have similar wording to convey the same message. Blease Medical Equipment has been producing anaesthetic machines for many years. We have used length and diameter indexed tubes for a very long time, as have all our competitors.

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1. Walmsley AJ, Holloway J. Transposition of rotameter tubes [letter]. *Br J Anaesth* 1998; 80: 124-125.

Remifentanil

Editor,—We read with interest Dr Dresner and colleague's letter[1] and Drs Morton and McClure's reply[2] regarding the use of remifentanil as part of an epidural test dose.

Morton and McLure disagree with the possible use of remifentanil because of "unknown risks."

Glycine is present in a concentration of 13 mg per 1 mg formulation of Ultiva (remifentanil) and the drug's data sheet states that this is "contraindicated for epidural and intrathecal use."[3] It has been shown to be neurotoxic in rats,[4] to cause encephalopathy in high doses,[5] and to cause reversible motor impairment after intrathecal delivery.[6] Clinical trials by Glaxo Wellcome in dogs showed that when injected intrathecally the buffer alone (glycine) caused hind limb muscle twitching, pain, and convulsions in high doses. Interestingly no such effects were seen with the remifentanyl/glycine preparation (Lupton S, personal communication; Glaxo Wellcome plc).

Glaxo Wellcome plc are currently developing a glycine-free preparation, and trials are under way in the USA looking at its epidural and intrathecal use.

In view of the above known risks we feel that the use of remifentanil for axial blocks is currently contraindicated.

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1. Dresner M, Adams M, Klein H. Ropivicaine test dose in extra dural anaesthesia. *British Journal of Anaesthesia* 1997; 79: 813
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Sevoflurane for intubation of an infant with croup

Editor,—Barker describes his routine use of sevoflurane for inhalational induction in children with difficult or "easy" airways [1] We would like to report its use in the acute situation for intubation of a 22 month old, 15 kg male infant with "croup."

The history was complicated but included several days of fluctuating stridor during which an opinion had been obtained from a consultant otolaryngologist with a special interest in infants. A lateral *x* ray of the infant's neck had shown subglottic narrowing. On the day in question the stridor had worsened and it was agreed by all concerned that urgent intubation was now necessary.

The boy was brought to the anaesthetic room resting over his grandfather's shoulder. An experienced surgeon was in attendance. Induction of anaesthesia was with sevoflurane in oxygen 8 litres/min using an Ayres' T-piece and face mask with the child seated upright on his grandfather's lap. We started at sevoflurane 4%, increasing to 6% and then 8% when we were confident this would be tolerated. As soon as the child was judged adequately anaesthetised, a 20G cannula was inserted into an arm vein. Pulse oximetry, ECG, and non-invasive blood pressure monitoring were started. Intubation was attempted under deep oxygen–sevoflurane anaesthesia. At laryngoscopy a normal epiglottis and vocal cords were seen. A size 4.0 mm plain tracheal tube was chosen. Initial attempts at intubation failed because of the subglottic obstruction. It was easy to ventilate the infant's lungs using a mask and oropharyngeal airway, so atropine 150 µg and suxamethonium 30 mg were given intravenously. The trachea was intubated by the more experienced paediatric anaesthetist (APM) using an uncut 4.0 mm plain tracheal tube (Portex). Pushing the tube past the subglottic narrowing required significant force and there was no leak around the tube. Anaesthesia was continued with intermittent positive pressure ventilation using atracurium and isoflurane, and the infant was transferred to the regional paediatric intensive care unit for further management.

Viral croup or, more properly, acute laryngotracheobronchitis, is usually caused by parainfluenza virus types I and II, although other viruses have been implicated. It affects children between the ages of six months and three years, with a peak age of two years. Acute laryngotracheobronchitis may affect the entire laryngotracheobronchial tree, but inflammation of the subglottic region—the narrowest portion of the upper airway in infants—produces the typical signs and symptoms.[2] This results in gradually worsening inspiratory stridor progressing to fatigue and ventilatory failure If medical treatment fails to relieve ventilatory distress, an artificial airway must be considered. The current recommendation is inhalational induction with carefully titrated halothane in 100% O_2 and intubation performed with the child breathing spontaneously.[3]

We believe that this is the first report of the use of sevoflurane under these circumstances. Its use has also been described for the management of the difficult airway in adults in whom awake intubation is not possible,[4] but not in those in whom stridor was a feature. Barker also describes the use of sevoflurane for children with difficult airways resulting from anatomical problems,[1] but not from acute stridor. Inhalational induction of general anaesthesia is often used in children with, until recently, halothane as the preferred agent. The low blood gas partition coefficient (0.6–0.7) and pleasant, non-pungent odour of sevoflurane allow rapid smooth induction. Various investigators have described the induction characteristics of sevoflurane and halothane in children. Black and colleagues suggested that sevoflurane is better than halothane at providing a pleasant rapid induction without any airway complications and being free of appreciable effects on pulmonary ventilation, circulation, and neurological function.[5] Epstein and colleagues showed that induction of anaesthesia was faster with sevoflurane than with halothane, and that vital signs were more stable. They concluded that sevoflurane was an excellent agent for inhalational induction of anaesthesia in children [6] However, it must be remembered that because of its low blood–gas partition coefficient, awakening will also be rapid. Once induced with sevoflurane, there is the theoretical risk of the child becoming "light" if there is difficulty securing an airway.

On the basis of our single experience we suggest that sevoflurane is a suitable choice of agent for the inhalational induction of anaesthesia in infants with stridor who require intubation. We recommend, however, that any anaesthetist using sevoflurane in this way should be experienced in its use for the inhalational induction of anaesthesia in infants undergoing routine surgery.

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1. Barker I. Is sevoflurane replacing halothane? [letter] *British Journal of Anaesthesia* 1998; **80**: 123.
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Risk factors for cardiovascular death

Editor,—The excellent case–control study by Howell and colleagues[1] does, with considerable authority, confirm the validity of previous cohort studies which identified both previous myocardial infarction and renal impairment as independent risk factors for cardiac death following anaesthesia and surgery. Their findings that diabetes mellitus is not even a univariate predictor is interesting, but not surprising and warrants further consideration. They postulate that there may have been some bias in attributing deaths in diabetic patients to their diabetes rather than to cardiovascular complications. However, it is generally accepted that the reverse is true,[2] and therefore this is not the explanation.

Perioperative cardiac complications are almost universally associated with the presence of underlying coronary artery disease. In order for a risk factor to reliably predict a cardiovascular event within a 30 day period, it must be able to select a population in which important coronary artery disease exists at the time. A history of angina, previous myocardial infarction, previous heart failure, and/or peripheral vascular disease will, with a reasonable degree of certainty, select such a population. Intuitively, a history of diabetes will not. Although coronary artery disease is the leading cause of death within the diabetic population, its presence is related to the duration of disease and not just the diagnosis. Thus, although a diagnosis of diabetes will reliably predict long term cardiovascular events, it will not do so over the short term. Many diabetic patients undergoing surgery will not have coronary artery disease, and this I suspect is the explanation for the poor performance of diabetes as a predictor of cardiovascular death in Howell's study.

All this does not mean diabetes is not a risk factor, but rather other elements—in particular duration of disease and age of the patient—must also be incorporated before assigning risk. For example an elderly type II non-insulin-dependent diabetic could be considered at risk five years after the diagnosis of diabetes. However a type I insulin dependent diabetic may not be at significant risk of coronary artery disease until 15 to 20 years after diagnosis (although at this time he may still be younger than the previous patient). Although this makes risk prediction a more complex issue, accurately predicting a major cardiovascular event over the short term in a well controlled patient undergoing elective surgery is a complex and difficult task.

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Editor,—We are grateful for these comments on our study and for the opportunity to reply. The proposed explanation for the failure of diabetes mellitus to predict cardiovascular death following anaesthesia and surgery may well be valid. As we pointed out, if this is the case, then the duration of diabetes should be included in the predictive model. We did not collect these data on our subjects and are therefore unable to test the hypothesis that including the duration of diabetic disease would improve the predictive power of the model. Adding this continuous variable would, of course, increase the number of adverse outcomes which needed to be studied to achieve adequate statistical power. Nevertheless, in the light of these comments, duration of diabetes should probably be examined as a potential predictive variable in future studies of perioperative risk.

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Walking extradurals

Editor,—We read with interest the editorial by Elton, Ali, and Mushambi on "walking extradurals" in labour[1] and concur with their cautious assessment of the benefits of the combined spinal–extradural technique (CSE) for the obstetric patient. We too feel that inadvertent insertion of an extradural catheter into the subarachnoid space through a spinal needle puncture site is unlikely and would offer other more plausible mechanisms for the occasional unexpectedly high block obtained with the CSE technique. Blumgart and colleagues showed comparable cephalad extension of a pre-existing subarachnoid block in obstetric patients after extradural injections of saline or bupivacaine,[2] concluding that the enhancement of the block was largely a volume effect. In an animal study, Swenson and colleagues found markedly increased morphine concentrations in cerebrospinal fluid following administration of extradural morphine adjacent to a dural puncture, compared with a control group.[3] These studies suggest that there may be fundamental differences in the effects of drugs delivered extradurally using CSE compared with traditional extradural analgesia, and reinforce the need for cautious incremental dosage of local anaesthetics and opioids when this technique is employed.

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1. Elton CD, Ali P, Mushambi MC. "Walking extradurals" in labour: a step forward? *British Journal of Anaesthesia* 1997; 79: 551–4.

2. Blumgart CH, Ryall D, Dennison B, Thompson-Hill LM. Mechanism of extension of spinal anaesthesia by extradural injection of local anaesthetic. *British Journal of Anaesthesia* 1992; **69**: 457–60.
3. Swenson JD, Wisniewski M, McJames S, Ashburn MA, Pace NL. The effect of prior dural puncture on cisternal cerebrospinal fluid morphine concentrations in sheep after administration of lumbar epidural morphine. *Anaesthesia and Analgesia* 1996; **83**: 523–5.

Editor,—Thank you for the opportunity to reply to this letter.

Drs Murray and Birks have rightly pointed out that administration of fluid into the epidural space immediately after a subarachnoid block at the same dermatome can result in an unexpectedly high block.

The most likely explanation for an unexpectedly high block following the epidural administration of drugs after combined spinal epidural is the passage of the epidural catheter into the cerebrospinal fluid following inadvertent dural puncture with the Tuohy rather than the spinal needle. Therefore care should be taken with any epidural to detect subarachnoid placement of the epidural catheter and minimize the effects of such administration. This risk should be the same whether this follows an epidural or a CSE. A further possibility is subdural placement of the epidural catheter and subsequent erosion of the catheter through the arachnoid mater into the CSF.[1] [2] It is unclear what the incidence of this problem is and whether it is more likely following a CSE.

The effect of fluid in the epidural space on the height of spinal anaesthetic administration is well known, particularly where subarachnoid administration follows an epidural top up rather than precedes it. Cephalad spread might be expected to be greater with a hydrophilic drug such as morphine rather than a lipophilic drug such as fentanyl, which rapidly fixes to neural tissue.[3] Consequently subarachnoid morphine, which was used in the study quoted by Drs Murray and Birks, is rarely used in United Kingdom as an analgesic for labour. However, the effect of epidural fluid administration on spread of subarachnoid morphine may be relevant where CSE with morphine is used for caesarean section rather than labour. Nevertheless we would recommend avoiding epidural top ups for a minimum period of 30 minutes after CSE using fentanyl.

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1. Elliott DW, Voyvodic F, Brownridge P. Sudden onset of subarachnoid block after subdural catherization: a case of arachnoid rupture? *British Journal of Anaesthesia* 1996; **76**: 322–4.
2. Richardson MG, Wissler RN. Unexpectedly high spinal block in obstetrics. *British Journal of Anaesthesia* 1996; **77**: 806–7.
3. Mather LE. Analgesic drugs. In: Nimmo WS, Smith G, eds. *Anaesthesia*. Oxford: Blackwell, 1989: 73–104.

Editor,—We read with interest but some confusion the editorial by Elton, Ali, and Mushambi: "Walking extradurals" in labour: a step forward?[1]

First, the paper focuses on ambulation in labour principally in association with combined spinal–epidural (CSE) analgesia, and not with epidurals per se. We submit the editorial would be more correctly entitled: "Ambulatory (or 'walking') regional analgesia in labour."

Greater freedom of movement and coordination, including ambulation, is possible only with a highly selective neuronal block. With the synergistic opioid-bupivacaine combinations used today, such highly selective blockade is achievable only by minimising the total dose. One of the fundamental advantages of a CSE is that such a block is produced almost instantly with a far smaller initial dose, compared with an epidurally administered initial dose.[2] With CSE, a minuscule first dose is possible because the intrathecal compartment contains nerve axons with minimal epineural tissue and vascularity compared with the epidural space. Thus, initial intrathecal administration fulfils the old pharmacological dictum: the smallest effective dose of any drug is the best dose.

For almost 17 years the bupivacaine–opioid CSE technique has been researched and refined in several countries. It is used not only in obstetrics, but also in many other areas of anaesthetic practice.[3] To date CSEs have been used for analgesia in more than 10 000 parturients at Queen Charlotte's Hospital[4] (and Crowhurst JA, Plaat F, unpublished data) and for analgesia and surgical anaesthesia in many more thousands of patients in Europe and elsewhere.[3]

Apart from successfully allowing > 80–90% of labouring parturients to be ambulant, one of the most significant features of the low dose bupivacaine-opioid CSE technique is the omission of the traditional epidural "test dose."[4–7] This aspect was not addressed by Elton and colleagues.

The authors state that the first use of any epidural catheter must be under the direct supervision of trained personnel, particularly when a test dose has not been given. This philosophy, based on traditional test doses, disregards the relative safety of today's low dose combinations, even when they are given through misplaced or displaced catheters.[8] [9] Small doses of bupivacaine (2.5–10 mg) and fentanyl (20–25 μg) produce very predictable effects when given incrementally into the intrathecal or vascular compartments. Such effects are mild when compared with the potentially catastrophic sequelae which may accompany a positive traditional test dose of 15–20 mg of bupivacaine, or 45–50 mg of lignocaine with adrenaline. Of course, careful supervision of all drug administration is mandatory.

Further, the use of a traditional test dose removes any chance of achieving a selective block, which will permit safe ambulation and other coordinated motor activity.[10] [11]

Second, as your authors acknowledge, meningitis has been associated with CSE, but also with traditional epidural and spinal methods.[12] [13] We dispute, however, that any "excess incidence" of meningitis has been shown with CSE. Case reports suggest that infectious complications are almost always associated with avoidable factors and careless technique.[14–16]

We disagree strongly with the statement that traditional epidural techniques are "inherently safe." Careful patient selection, examination, and scrupulous attention to asepsis and antisepsis are mandatory; and *no* central, neural blocking technique is for the casual or inexperienced operator. Even with these safeguards, there is always some risk of infection, which for spinal and epidural is undoubtedly greater than for other injection methods such as intravenous, intramuscular, and so on.

Third, improved analgesia, ambulation, and increased maternal satisfaction have inevitably increased patient demand. But this should not be a reason to limit the availability of safe, effective pain relief, which at last is beginning to be regarded as a basic human right.[17] Anaesthetists today should be aware that demand for acute pain services is increasing, and that more resources and personnel need to be directed to providing such services.

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British Journal of Anaesthesia 1998; **80**: 703–705

BOOK REVIEWS

Handbook of cardiac anaesthesia and perioperative care. A Demythologised Approach. JOHN D. WASNICK. Published by Butterworth-Heineman, Boston. Pp. 388; indexed, illustrated. Price: £37.50.

This single author text is written by an attending anaesthesiologist from the cardiac anaesthesia group in Dallas. It is aimed at "the anaesthesiologist who infrequently provides cardiac care or is returning to cardiac anaesthesia practice." These practitioners are fortunately rare in the United Kingdom. For the European market, the text would be targeted at the specialist registrar about to embark on his attachment in cardiac anaesthesia.

The book is written in an easy narrative style and can be read in its entirety at two or three sittings. While the range of subjects covered is comprehensive, the depth of detail is not—nor is it intended to be. Useful suggestions for further study are instead provided in a fairly extensive bibliography containing many of the most important publications in the field over the last decade. The chapters are well laid out, dealing initially with routine uncomplicated cardiac operations, and moving on to more specialised subjects such as transplantation, arrhythmia surgery, and transoesophageal echocardiography. The "demythologised" approach taken by the author—"keep it simple stupid!"—works well, with plenty of good practical advice in contentious areas such as weaning the heart from cardiopulmonary bypass. The accent on the well founded core principles of cardiac anaesthesia also protects the book from the problem of rapid obsolescence that is inherent in many textbooks. A very useful addition in this context is an up to date list of web sites of particular relevance to the cardiac anaesthetist.

The book contains a large number of black and white photographs. Some of these are useful in outlining the stages of a cardiac operation, but the clarity could be improved. Some are superfluous. The same picture of a Swan Ganz introducer inserted into the neck is used twice (pp 29 and 82) and even the most inexperienced cardiac anaesthetist gains little from a photograph of a double lumen subclavian catheter. Fewer illustrations, perhaps in colour and certainly better labelled, would greatly improve the overall clarity of the text.

There are a few omissions, but you have to look hard to find them. Most cardiac operations are still performed under induced hypothermia. Temperature monitoring and the problems of hypothermia receive little attention. Blood conservation is also an integral part of modern cardiac anaesthesia. The limits and potential problems of normovolaemic haemodilution are covered, but the use of mediastinal retransfusion, cell salvage, and autologous transfusion could usefully be included.

This book provides a fascinating insight to the relation between cardiac surgeons and anaesthetists in the USA. The author seems to have a great distrust of the former, who are depicted as being only too ready to blame the anaesthetist for any adverse perioperative outcome. Apparently we need to "be cognizant that whenever a haemodynamic change occurs, even to the slightest degree, the surgeon is most likely to ascribe any adverse outcome in the patient to that event and anaesthesia will be blamed" (p. 117). If femoral cannulation is required for blood pressure measurement, the author recommends that a surgeon be asked to perform the procedure. Then, "having been involved from the start they have a sense of participation in the management of any problems that may result" (p. 71). There are numerous similar examples throughout the text. The author to an extent recognises his distrust, and in the preface asks to be forgiven if a ray of cynicism shines through. It is unfortunate that the cynicism borders on a paranoia that detracts from the enjoyment of this otherwise very useful book.

Would I recommend this text to our trainees? Indeed I would, for it has much to offer—but only if you enjoy your cardiac anaesthesia with a large dose of cynicism!

G. N. Russell

Pain Relief in Labour. R. RUSSELL, M. SCRUTTON, J. PORTER, AND F. REYNOLDS (editors). Published by BMJ Publishing Group, London Pp. 252; indexed; illustrated Price £24.95.

Aimed at anaesthetists, midwives, general practitioners, and obstetricians who wish to be informed on a broad front in order to give mothers a balanced view of the options available for pain relief in labour, this book succeeds admirably. It contains information on the pros and cons of psychological and physical methods, including TENS, massage, water baths, and aromatherapy. Regional techniques are also covered comprehensively. The importance of information being transmitted antenatally is emphasised, referral of patients with special problems being highlighted

The publication of this book is particularly timely with the doctrines of "changing childbirth" being well versed in the community. In places, however, it is slightly disingenuous—an example being that one should aim to have a working regional block in all women who are likely to have an instrumental delivery, if only we (or our obstetric/midwife colleagues) were better at predicting that outcome!

I would have liked more to have been included about the conditions under which midwives can top up epidurals and perhaps whether there will be difficulties for midwives having to be aware of the different concentrations of bupivacaine and ropivacaine used. I have concerns over the impression that "respiratory depression is not a major problem in the parturient who is usually young and fit and less likely to be neglected by carers than is a patient on a postoperative ward," Eternal vigilance is required to ensure against disasters

The chapter containing advice on pre-empting and managing complaints is very apposite. In view of the increasing number of questions and complaints I think this could be expanded in a second edition. The importance of audit and good record keeping are rightly emphasised.

The authors should be congratulated on their book which is a must for every delivery suite.

G. M. Cooper

Anaesthesia and Intensive Care in Hong Kong, Evolution and Present Position. Z. LETT AND R. L. JOY-WAH. Published by The Centre of Asian studies, The University of Hong Kong, Hong Kong. Pp. 165; indexed; illustrated. Price £6.50.

This monograph was written by two people who have had a long association with the development of anaesthesia in Hong Kong. Nobody is more qualified than Dr Lett—who is regarded as a doyen in Hong Kong anaesthesia—to write a book on the evolution of anaesthesia and intensive care in this city.

The book has 15 chapters, with an introduction written by the deputy director of the University of Hong Kong Postgraduate Medical Education and Training School. The chapters begin with a description of the problems of providing an anaesthesia service and training in the early 1950s, and progress to record the assistance obtained from various international connections, in particular the then Faculties of Anaesthetists of the Royal College of Surgeons of England, Ireland, and Australia, in the training in anaesthesia. The setting up and development of anaesthesia, intensive care units, pain service, academic departments in the two medical schools, and finally the establishment of the Hong Kong College of Anaesthesiology (HKCA) in par with the other specialties under the Hong Kong Academy of Medicine is then described. The aims of this College are to achieve and maintain a training and examination system that is able to stand alongside the best institutions in the world. The other half of the book is devoted to photographs of old friends, visitors, and anaesthetists in Hong Kong, meeting programmes, lists of members of various committees, and some old personal correspondence.

It is a book for light reading: it will interest those who had past connections with Hong Kong medical history, and any who are concerned with the development of anaesthesia and intensive care in Asia.

C. S. T. Aun

Peri-Operative Transfusion Medicine. B. D. SPIESS, R B COUNTS AND S. A. GOULD (editors). Published by Williams And Wilkins, Baltimore, Maryland, USA. Pp 607; indexed, illustrated. Price £70 00.

This is an excellent book. Despite the fact that it has 50 contributors, it maintains a consistent style and approach throughout.

The majority of contributors are surgeons, anaesthetists, or physicians. All acknowledge that there has been a transition from bloodbanking to transfusion medicine and this transition is reflected practically in all the chapters. The book is divided conveniently into sections and within each section there are various chapters, addressing different aspects of transfusion practice.

An introductory section is followed by a section devoted to blood service interaction with surgical care. A whole chapter is devoted to the physiological basis for the transfusion trigger, within which all aspects of oxygen delivery and consumption are well addressed. There are also excellent chapters on platelet production and physiology and on the physiology of haemostasis. Alternatives to blood transfusion including preoperative donation, normovolaemic haemodilution, and the use of erythropoietin are all discussed appropriately The chapters on quality control of hospital transfusion practice and legal duties to patients and dispute resolution are perhaps a little inappropriate for United Kingdom readers but do throw some interesting light on problems that are encountered in the USA.

The section on preoperative preparation covers topics such as resuscitation, coagulation monitoring, and management of patients with hypercoagulable states. An entire chapter is devoted to the management of patients receiving anticoagulant treatment, but it is rather disappointing. It alludes to the fact that potentially 5% of patients in their 70s will be receiving oral anticoagulation. However, more specific discussion of the management of these patients pre- and postoperatively is a little sketchy.

The fourth section includes chapters covering such topics as oxygen supply and demand (again), conservation techniques, cell salvage, massive transfusion, hypothermia and haemorrhage, use of fresh frozen plasma (FFP), pharmacological approaches to decreasing bleeding, and fibrin glue. There are some useful algorithms in the chapter on massive transfusion which attempt to clarify the use of coagulation tests and platelet and coagulation factor replacement in these difficult situations.

The chapter on FFP use is also informative and practical; it yet again reminds us that FFP remains "one of the most inappropriately transfused blood components." The transfusion risks which this product carries are discussed and mention is made of the development of virally inactivated FFP. Attention is drawn to the relatively high cost of a product that will impart only small benefit, but the comment is made that once viral inactivated FFP is available, it will be difficult for clinicians to continue to use untreated FFP. The chapter on the use of fibrin glue was interesting, though perhaps a little esoteric for discussion as a separate chapter in this volume

Section 5 contains chapters devoted to transfusion for specific surgical specialties. The chapter on transfusion and cardiac surgery is particularly good and discusses a variety of problems with coagulation in depth, as is reflected in the 579 references in this chapter alone. There are also useful chapters on transfusion for peripheral vascular surgery and for transplantation of liver, kidneys, pancreas, and lung. The use of transfusion for trauma and burns is well covered. Unfortunately, the chapter on transfusion for haemorrhage in paediatric patients is a little sketchy and does not refer specifically to neonates, who are the most highly transfused group of patients relative to their size. There is also a slightly macabre section in "Transfusion for neurosurgery," with recommendations for the management of brain dead patients for organ donation.

The final section comprises only two chapters and is devoted to postoperative transfusion decisions. The final chapter, entitled the "Transfusion decision," should be compulsory reading for all involved in prescribing transfusions. It could well have been an opening chapter for this book, however, it summarises excellently the opinions of all authors of the preceding chapters. We are reminded that "the decision to transfuse a patient, with either a red cell product or coagulation component, should not be taken lightly."

This volume will make a very useful addition to all medical libraries. It gathers together a large amount of information that is not usually found within a single volume. It is, unfortunately, predominantly a reflection of practice within the USA and for this reason most of the guidelines referred to are not United Kingdom guidelines. However, there is less deviation nowadays in the practice of transfusion medicine between the United Kingdom and the USA and what differences there are do not detract from the usefulness of this volume.

J. K. M. Duguid

A Simple Guide To Blood Gas Analysis. P. Driscoll, T. Brown, C. Gwinnutt, and T. Wardle. Published by the BMJ Publishing Group, London. Pp. 191; indexed; illustrated. Price £20.

The medical curriculum gets more and more crowded as different specialties are promoted by their practitioners. Our medical schools are filled with professors of ever more circumscribed medical subspecialties. Meanwhile, medical students are not taught, or fail to learn, about many topics that are important in the everyday management of medical and surgical patients on the ward. Whether or not subspecialty professors would agree, anaesthetists place much importance on the ability to interpret blood gas results. Driscoll and colleagues are right when they say blood gas results cause confusion and anxiety; and they are also right when they ascribe this confusion to the tendency of teachers to launch into equations. They have written a useful little book, which will enable their intended readership—medical students, resident doctors, and nurses—to take an arterial sample and interpret the result.

The layout has the clarity we have come to expect from the BMJ Publishing Group, and there are boxed lists and key points. There are plenty of quizzes, both within and at the end of chapters. Readers are advised to take a break before each end of chapter quiz, which is excellent advice, and means that by the time they have finished the book they have been told to take a walk, two cups of coffee, a sandwich, a cup of tea, a run (and a shower), and a well earned rest.

I recommend this book for medical students especially (it is too simple for anaesthetists), but it is a missed opportunity Authors who write as clearly and with such enthusiasm as this should not miss out the Henderson-Hasselbalch equation completely, and dismiss logarithms with the footnote, "If you are interested, the pH is the negative logarithm of the hydrogen ion concentration. Still interested?" This makes the book simple to the point of flippancy, and it does not deserve that. We have to instil understanding, not just a superficial familiarity.

There is plenty of space for improvement, because although some of the cartoons work well, others do not. For example, there is a series of cartoons intended to illustrate the balance between various disturbances and compensations—but there is nothing to make a particular picture stick in the mind. There is a whole page illustration of K^+ coming out of cells and H^+ going in. I am sure that Driscoll and colleagues could have explained the Henderson-Hasselbalch equation, as well as introducing some of the other acid–base diagrams (a book on acid–base balance without Sigaard-Andersen in the index?), in this sort of space. When they write the second edition, they should also stick to their own given definitions of "ventilatory" and "respiratory"; by chapter six, respiratory is being applied to rate and depth as well as to alkalosis.

N. W. Goodman

The Clinical Practice of Critical Care Neurology. E. F. M. Wijdicks. Published by Lippincott-Raven, Philadelphia. New York. Pp. 419; indexed; illustrated. Price £80.00.

In this book, the author, who is professor of neurology at the Mayo Medical School, reviews critical care in the neurological intensive care unit. He emphasises day to day management and writes for neurologists, intensivists, anaesthetists, and neurosciences nurses; the book obviously reflects his extensive experience in his specialist field. It comprises 30 chapters, divided into four parts, encompassing general principles of management; equipment; management of specific disorders; and finally management of systemic complications in critically ill neurological patients.

The first eight chapters form part I of the book This is a detailed account of routine nursing and physical care of the patient, management of pain and agitation, airway and ventilation, cardiovascular status, thrombolytic treatment, and intracranial pressure. American clinical practice (with the use of American drug names) is reflected in these chapters, and does not altogether correlate with current United Kingdom practice. A section on conveying information to the patient's family is an unusual inclusion, with an amusing paragraph on the "VIP syndrome." The chapter on airway management and mechanical ventilation is well written but from a neurologist's background, and may prove tedious for the anaesthetic reader. Some indications for ventilation in patients with ischaemic stroke and subarachnoid haemorrhage would also be contentious in current British practice. Anticoagulant treatment covers prophylaxis of deep vein thrombosis and treatment of acute embolic stroke, including intra-arterial thrombolytic agents. The chapter on intracranial pressure (ICP) management gives an excellent resumé of the physiology, and the general and specific measures available to manipulate ICP; however, a greater emphasis on the maintenance of adequate cerebral perfusion pressure as the over-riding management principle would have been more in line with United Kingdom practice.

Part II encompasses monitoring devices ranging from clinical assessment using the Glasgow coma score to ICP, PA, and SjVo, catheters, and is well illustrated. Diagnostic procedures, including transcranial Doppler ultrasonography, EEG measurement, and CSF examination—areas perhaps less familiar to the anaesthetist—are very clearly set out, and their usefulness and limitations discussed.

Part III is the largest section of the book, totalling 15 chapters which describe the management of specific neurological disorders. The clinical recognition and investigation of aneurysmal subarachnoid haemorrhage (SAH) is very well documented. However, some management aspects—including pain relief, sedation, and mechanical ventilation for poor grade patients, including those who have re-bled—reflect the American practice of admitting all SAH patients to the intensive therapy unit, a practice not undertaken in Britain. Unfortunately, the neurosurgical management and postoperative care (including treatment of delayed ischaemia after successful clipping of the aneurysm) is not within the scope of this text, although these patients comprise a sizeable number of admissions to British neuro-intensive care units. The subsequent chapters on intraparenchymal haemorrhage, stroke, and infarction are well written, with a wide variety of computerised tomographs and magnetic resonance images to illustrate the clinically orientated text, and an interesting comparison of aggressive interventional management. The remaining chapters cover the clinical course, investigation, and management of intracranial infection, epilepsy, and neuromuscular disorders, including Guillaine-Barré syndrome with autonomic disturbance and myasthenia gravis. A useful evaluation of current treatment regimens is included. The final chapter in part III describes the clinical diagnosis of brain stem death, and the validity of confirmatory laboratory tests. This is an excellent chapter, with one exception. The author refers to "respiratory-like movements and agonal breathing patterns," which will confuse the inexperienced reader. These relate to truncal movements, probably a reflection of spinal cord terminal hypoxia, and to invoke the term respiration may well fail to keep the definition of the apnoea test clinically succinct.

Part IV addresses the systemic complications of critically ill neurological patients, including pulmonary, cardiac, acid–base, and hypo/hypertonic disorders, gastrointestinal complications and nosocomial infections. I enjoyed these chapters, which are full of clinical fact and practical advice. The chapter on acid–base status and salt and water homeostasis is particularly good. This difficult topic is discussed with erudition and I would commend the author for his clarity. It is marred only by the mislabelling of one of the tables. The book closes with useful tables for titrating strategy.

This book is of a high standard, well written, and extensively illustrated. Each chapter has a highlighted "conclusions" paragraph, which provides a useful resumé. The hard backed text is accompanied by a pocket sized notebook of selected tables and figures for handy bedside reference. It proves a very interesting, highly informative, and well referenced text for those who are interested and experienced in this specialist field, with an opportunity to draw a comparison with American practice. For those in training, the book contains a wealth of diagnostic, investigative, and management information on critical care in neurological problems, although they may be confused by the differences in British and American practice. The book inevitably has a bias to neuromedical conditions, although surgical interventions are mentioned. It is a good text for British neuro-intensivists, but only partially covers the spectrum of neurological and neurosurgical conditions managed in units in the United Kingdom.

J. R. Dalton

ERRATA

In the paper by T Asai and colleagues in the January issue (volume 80, pages 63–7) various errors occurred in the production process. The editorial team and publishers apologise for these errors, which were as follows:

Page 63, left column, para 1: the last sentence should read "...there is some evidence for lack of enhancement of the effect on respiration."

Page 65, in the legend to fig 2, line 5, the phrase "The point (P1) on the isobole is..." should read "The point (P2) on the isobole is..."; and "The actual ED_{50} of the mixture (P2)" should read "The actual ED_{50} of the mixture (P1)."

Page 65, left column, para 3: the last sentence should read "In addition, even if higher doses of these drugs..."

Page 66, para 4 should end "t values of only 4–5 compared with the $t > 6$ required to meet Armitage and Berry's[37] recommendation that g should be < 0.1 in the simplified form of the Fieller equation used by Tallarida, Porreca and Cowan.[15]"

Page 66, para 5: the references to the "Bootstrap" technique, "37–39", should read "38–40".

In the paper by P B Ali and colleagues in the February issue (volume 80, pages 245–7), an error appeared in the summary:

Page 245, summary, line 13: "20 mg" should read "20 ml".

The publishers extend their apologies to the authors for this error.

"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

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EDITORIAL I

New considerations in pharmacokinetic variability: within-patient variability over time

The purpose of performing pharmacokinetic studies is to obtain data that can guide our predictions of the dose of a drug that will be needed in future patients. If these data are to be an accurate guide to therapy, the patient characteristics that affect drug disposition must be taken into account; therapy in patients with a particular condition must be guided by results in similar patients.

To advance this aim, it is usual to study discrete groups of patients who differ from each other in one particular respect, be it age, sex, body weight, the extent of renal or hepatic function, or more transient patient features such as temperature, or use of a particular anaesthetic. Such studies on discrete groups are the foundation of most of our present knowledge of pharmacokinetics. Consider a simple example — the effect of advancing age on the clearance of non-depolarizing neuromuscular blocking drugs. It was by studying two groups, similar in all respects but age, that the plasma clearance of pancuronium was shown to be decreased in the elderly.[1] This finding was subsequently shown to extend to vecuronium,[2 3] rocuronium,[4] and to the organ-dependent clearance of atracurium,[5] in each case using the same study design with two comparable groups. The same design has served well to define the effect of obesity on the pharmacokinetics of the neuromuscular blocking drugs. Thus two groups of patients, one obese and the other of normal weight, were given a bolus dose of atracurium 0.2 mg kg^{-1}, and it was found that plasma concentration was consistently, and significantly, higher in the obese than in the normal patients.[6] Consequently, when expressed in absolute volume terms (not normalized for body weight) the total volume of distribution and clearance of atracurium were little changed by obesity.

The traditional method of studying two discrete groups is statistically efficient, and thus is able to detect quite small differences between groups. For example, it was by studying two groups of patients, one healthy and one suffering from chronic renal failure, that the elimination half-life of cisatracurium was found to be increased from 30 to 34.2 min in renal failure.[7]

Studies that examine in detail the effect of a single factor on pharmacokinetics leave at least two problems for the clinician. First, there is considerable variability between individuals, so that when presented with a patient of known age, weight and creatinine clearance, the pharmacokinetic parameters and hence the resulting plasma concentration profile can be predicted only within quite wide limits. Thus it is recognized that the serum digoxin level may be in the toxic range, and the patient may be suffering from digoxin toxicity, even when a pharmacokinetic model taking that patient's characteristics into account predicts a value in the therapeutic range.[8] Second, patients often present with a combination of ills that defies such a neat characterization; for example, a patient may be elderly and mildly overweight, and have a degree of renal dysfunction that falls short of end-stage renal failure. Such patients would not meet the inclusion criteria of traditional discrete-group studies; the pharmacokinetic behaviour of such patients is left undefined.

The anaesthetist is fortunate, perhaps, in that many of the drugs used can be titrated to achieve a desired effect; we have an increasing number of drugs, such as remifentanil, with pharmacokinetics that render them suitable for flexible titration.[9] The problem is acute, though, for drugs that cannot be so readily, or safely, titrated to an observable effect, and that have a low therapeutic index. Apart from digoxin, obvious examples are theophylline, the aminoglycoside antibiotics and immunosuppressant drugs such as cyclosporin; in the case of these drugs, dose adjustment has to be guided by measurement of plasma drug concentration in the individual patient.

At least two other approaches may be helpful. First, one can adopt a population-based approach to pharmacokinetic analysis. This focuses on the variability between individuals as a matter of primary interest; and it provides the statistical methodology to allow something to be said about the pharmacokinetics of patients seen in routine clinical practice. Indeed, it was to facilitate the study of digoxin kinetics from routine patient data that this approach was conceived, more than two decades ago.[10] Population-based pharmacokinetic analysis has been thoroughly reviewed in a recent issue of this journal,[11] and it is likely to find increasing application in anaesthetic research. For example, it was using this method, with analysis of only a few blood samples from each of a large number of subjects, that the effect of age on the pharmacokinetics and concentration–effect relationship of cisatracurium was defined.[12] Likewise, a population approach to the pharmacokinetics of high doses of thiopentone in the head-injured patient was able to define a quadratic relationship between clearance and age, with a peak clearance at around 45 years.[13]

A second approach is to define the pharmacokinetic behaviour of a drug in the critically ill patient. Not only is this important in itself, but it sets a limit on any extremes that are likely to be encountered in routine practice. Thus it was demonstrated 15 years ago that the elimination half-life of atracurium is not significantly changed from the healthy value by the presence of severe hepatic and renal impairment[14]; this finding was recently confirmed for cisatracurium in patients undergoing hepatic transplantation.[15] It is clear that one is unlikely to meet a patient in whom the elimination half-life of atracurium much exceeds 20 min. Further support for this point was provided by data obtained from patients in the ICU, for cisatracurium and for the different isomer groups of atracurium.[16] In contrast, when a drug is dependent upon organ function for its elimination, the critically ill subject can yield pharmacokinetic parameters that differ greatly from those in the surgical population. Thus the mean value of the elimination half-life of rocuronium was found to be as high as 337 min in a group of 12 seriously ill patients[17]; this represents a three-fold increase over the value of 108 min in otherwise healthy patients undergoing routine anaesthesia, who were studied by the same authors. Our knowledge of the pharmacokinetics of vecuronium in patients in the ICU has been extended in this issue of the journal by Segredo and others.[18] In a series of critically ill individuals receiving artificial ventilation for adult respiratory distress syndrome, they found a value for vecuronium clearance of 2.5 ml kg^{-1} min^{-1} or less, at some time point, in four of the six patients. The estimates of mean residence time ranged from 123 to 586 min. The results illuminate early pharmacodynamic evidence of a prolonged recovery from vecuronium in the ICU.[19] A perhaps more important aspect of the present paper is that it adds a temporal dimension to pharmacokinetic analysis. Most pharmacokinetic studies look at each patient at one point in time. In this study, the authors obtained abundant plasma concentration data on two occasions in each of six individuals, and showed that clearance changed by a large factor. Moreover, the extent and direction of the change was unpredictable, and the authors could not plausibly relate the changes in vecuronium clearance to changes in renal or hepatic function.

Relatively few studies have addressed the issue of changes in pharmacokinetics over time. An exception was provided by Fisher and colleagues who documented the pharmacokinetics of rocuronium during liver transplantation.[20] The plasma concentration profile of rocuronium following two bolus doses (one given at the start of the anaesthetic, the other given soon after perfusion of the graft) could be better explained if clearance were allowed to take a different value following graft perfusion than in the earlier stages of the operation. Furthermore, not only did the plasma clearance differ according to the stage of the operation, but the estimate of interindividual variability in clearance increased after graft perfusion.

There are other studies of temporal variability in the pharmacokinetics of non-anaesthetic drugs. For example, the pharmacokinetics of vancomycin were determined twice in each of a series of critically ill infants aged 1–10 months.[21] It was found that between 2 and 8 days after admission to the ICU, the volume of distribution fell from a mean value of 0.8 to 0.44 l kg^{-1}, reflecting perhaps the effect of initial aggressive fluid resuscitation on the first value of volume of distribution. The authors also found, however, that while the mean value of clearance did not change significantly, there were considerable changes in the values in particular infants, ranging from a 50% increase to a 45% decrease. As in the present study, the authors could not relate these changes in clearance to changes in renal function.

Variability in the plasma concentration profile of a drug in the same subject on different occasions has also been studied for orally administered cyclosporin in renal transplant recipients.[22] The plasma concentration profile after a routine morning dose was evaluated in detail three times, at 2, 6 and 12 weeks after transplantation. The variability in peak plasma concentration, normalized to the dose given, was almost as great between different analyses within the same individual (an intrasubject coefficient of variation of 43%) as it was between different individuals (with an intersubject coefficient of variation of 47%). A similarly high intrasubject variability was found for other pharmacokinetic parameters.

An even more complicated example is given by ifosfamide, a prodrug that is metabolized to a series of compounds including a therapeutic alkylating agent and a toxic species.[23] The pharmacokinetics were evaluated in children during a series of courses of the drug, at two or three points, from a few weeks to a few months apart; the elimination half-life varied widely at different times in the same individual, from a 60% decrease to a 200% increase.

It is possible that such intrasubject variability over time will eventually be explained by documentation of temporal variations in the activity of important routes of disposition. For example, the activity of the cytochrome P450 3A (CYP3A) system has been found to vary in the newly transplanted liver.[24] In general, there is a rise in the activity of the enzyme in the first 10 days after operation; but where the liver has been obtained from a donor who had been treated with enzyme-inducing drugs, there is usually a fall from a high baseline to a lesser value. The plasma clearance of midazolam determined in such patients *in vivo* was strongly correlated with the activity of CYP3A measured *in vitro* in a biopsy specimen.[25]

For the present, however, studies such as that of Segredo and others challenge our conception of pharmacokinetic variability. In the population approach to kinetic analysis,[10 11] a pharmacokinetic parameter (such as plasma clearance) for any given individual is conceived to be composed of three elements: the "typical value", "fixed" effects and "random" effects. Thus the value is related to the mean value for the population — the typical value; the value for each individual is envisaged as differing from the mean by both "fixed" and "random" effects. The fixed effects are identifiable, measurable factors that plausibly determine the pharmacokinetic parameter, such as age and creatinine clearance, and that can be shown statistically to do so. The random effects comprise all the remaining variability in the individual values of the parameter that cannot yet be explained. The aim of population model building is to identify factors that explain pharmacokinetic variability in terms of "fixed" effects.

It is implicit in this approach that fixed effects may vary over time; for example the patient may develop renal failure, or hepatic function may improve. What Segredo and others have shown is that random effects on vecuronium clearance in the critically ill may vary widely over a short period. The objective of tailored dosing based on a previously established quantitative model is as elusive as ever. We must continue to rely on titration to effect where this is possible. For those few drugs where therapeutic effect cannot be achieved by individual dose titration and where the therapeutic margin is small, therapy must continue to be guided by measurement of plasma concentration.

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EDITORIAL II

Accidental i.v. injection of local anaesthetics: an avoidable event?

In this issue of the *British Journal of Anaesthesia*, Abouleish and colleagues[1] report a case in which accidental injection of ropivacaine into an extradural vein resulted in central nervous system toxicity and a seizure. The extradural catheter was inserted while the patient was in labour, but she delivered before it was used. She was then to undergo tubal ligation. In spite of a negative aspiration test and fractionating the total dose of ropivacaine 120 mg over 11 min, the patient had a tonic-clonic seizure. Fortunately, there were no life-threatening cardiac arrhythmias, the ECG indicating only a mild sinus tachycardia, and she came to no harm. The catheter tip was found to contain blood when it was removed. This is one of the first case reports of systemic toxicity with the clinical use of this recently introduced local anaesthetic agent and it raises several issues.

Is a negative aspiration test, particularly when done several hours after the extradural catheter has been placed, reassuring? The catheter had presumably entered an extradural vein, but the blood in the tip of it had clotted. This is the most likely reason for the negative aspiration test. Perhaps an initial flush of the catheter with saline followed by aspiration would have revealed the problem in this case, although it is interesting that a second aspiration test (always a wise precaution after the initial injection), done after the third bolus of ropivacaine, was negative. This suggests that the clot in the tip of the catheter was causing a flap valve effect, allowing injection of local anaesthetic into a vein, but preventing aspiration of blood.

Should an extradural catheter that has been inserted several hours before be "re-used" to establish a block? The answer is probably a guarded yes, but adequate tests must be used to determine if the catheter is within a vessel or has pierced the dura before the therapeutic dose of local anaesthetic is injected. What constitutes an "adequate" test to exclude catheter misplacement? The authors of the report used a test dose of ropivacaine 15 mg followed by a further 22.5 mg, 3 min later, but unfortunately this failed to warn that the catheter was within an extradural vessel.

Is a test dose of 2 ml of ropivacaine 0.75% (to exclude accidental subarachnoid block) followed 3 min later by a further 3 ml of the same solution likely to detect intravascular injection? The answer is probably not. Test doses of ropivacaine 22.5 mg failed to detect intravascular injection in two patients reported in a series by Morton and colleagues[2]; they stated that such a test dose is unsuitable in later correspondence on the issue.[3] The way in which the test dose is injected and the design of the extradural catheter may also influence the chances of a test dose giving a true positive result. The catheter used in this patient had two side holes and a closed end. These openings are usually about 1 cm apart, allowing the distal one to be misplaced and the proximal one correctly sited within the extradural space. A low-pressure, slow injection technique through such a catheter results in most of the injectate escaping through the proximal hole, whereas a high-pressure, rapid injection causes the majority of it to escape via the distal hole.[4] It seems logical, therefore, to inject extradural test doses rapidly under pressure when using multi-holed catheters. The reader should re-visit Bruce Scott's editorial on extradural test doses, which is as relevant today as it was when published 10 years ago.[4]

Ropivacaine has been shown to be less neuro- and cardiotoxic than bupivacaine in animal and human volunteer studies,[5 6] and this is one of its major advantages. The early symptoms of central nervous system toxicity occur before the cardiovascular effects and tend to be seen at a 25% greater dose of ropivacaine than bupivacaine.[6] However, this may result in a false sense of security when using a test dose of ropivacaine to detect intravascular injection, as exemplified by this case report. Unfortunately, accidental i.v. injection of local anaesthetic agents will occur from time to time even in experienced hands and despite all previous checks. Therefore ropivacaine, which has a higher threshold for causing life-threatening toxicity, is attractive, especially because resuscitation from such a catastrophe is more likely than with bupivacaine.[7] The key question is, how do we reliably detect i.v. injections of local anaesthetics before administering a dose that can cause systemic toxicity? In other words is there a state-of-the-art test dose? Ropivacaine toxicity may be less life-threatening than that of bupivacaine, but it is still better to prevent than treat it.

Extradural test doses have long been a contentious issue among anaesthetists and a variety of techniques (including the addition of epinephrine to the local anaesthetic,[8] rapid injection of 5 ml of bupivacaine 0.5%[9] and use of lidocaine 1 mg kg^{-1}[10] have been advocated. It is interesting to note that a test dose was used in most reported cases of high/total spinal anaesthesia, or serious systemic toxicity, during attempted extradural block.[4] Use of epinephrine with ECG monitoring may be an indicator of i.v. injection[8] but is not without risks, particularly in a patient with ischaemic heart disease or a pre-eclamptic woman in labour. Furthermore, Leighton and colleagues[11] found a 50% false-negative rate when epinephrine 15 μg was injected into a peripheral vein in labouring women. Rapid injection of bupivacaine 25 mg may fail to cause reliable signs and symptoms if injected i.v. in some individuals and, as Scott demonstrated on human volunteers, greater doses of ropivacaine than bupivacaine are required to cause central nervous system toxic effects.[6] Lidocaine is attractive for test dose use because it has a lower toxicity profile than bupivacaine, as quantified by the ratio of both the dose required to cause irreversible cardiovascular collapse and that required to produce convulsions. The ratio is 7:1 for lidocaine and 3:7 for bupivacaine.[12] A lidocaine 1 mg kg^{-1} i.v. test dose was shown to result in central nervous system symptoms in 19 out of 20 patients within 3 min[10] and such a dose administered intrathecally will not result in a particularly extensive spinal block.[13]

Dresner and colleagues[14] suggested using bupivacaine 10 mg initially as a test for accidental intrathecal catheter placement followed, a few minutes later, by a lidocaine 1 mg kg^{-1} test dose to detect accidental i.v. injection. However, this slightly cumbersome technique may be flawed as well. Prince and colleagues compared the effects of plain bupivacaine 8 mg given extradurally and intrathecally in labour and could only reliably discriminate between the routes after 10 min.[15]

Perhaps the most important reason that the patient reported in this issue did not have any serious sequelae after the i.v. injection of the extradural dose was because the total dose was given slowly over 11 min. It is important to emphasize that, even after negative test doses or aspiration tests, large doses of any local anaesthetic agent given by any route must be given slowly in divided doses to prevent a catastrophic event. In addition, because of the unpredictability of these events, an argument can be made for routinely using the least toxic local anaesthetic drugs available, such as lidocaine for short procedures and ropivacaine for longer operations, to reduce the risks of inadvertent i.v. administration. There is no doubt that lidocaine is a more forgiving drug than either ropivacaine or bupivacaine when an accidental i.v. injection does occur.

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EDITORIAL III

Could do better: statistics in anaesthesia research

Clinicians are familiar with the audit cycle. Medical practice is examined, improvements are suggested, and the practice is re-examined after a suitable interval, to allow the improvements to be made. There are difficulties with audit,[1] but all departments of anaesthesia can point to aspects of practice that audit has improved. In 1992, this journal published what was really an audit of statistical practice at the Anaesthetic Research Society.[2] All abstracts in the precirculated booklets for the three meetings in 1990 were examined. Simple statistical errors were grouped as errors in study design, or in choice of statistical method; errors in the presentation of variability; and errors in the presentation of probability. There had been studies of statistics in papers published in anaesthesia journals (for example, reference 3), but by the time a full paper is published, fellow workers, editors and referees have influenced the final version. The statistics presented in precirculated abstracts give a chance to assess the statistical knowledge of researchers in anaesthesia, which is otherwise impossible to assess: researchers are unlikely to answer multiple choice question papers sent out by the curious, even if they could spare the time. In the survey, 61 of 94 abstracts from 1990 presenting numerical information contained errors.

Five years on, we repeated part of this survey, looking at three booklets from 1995–1996. We did not repeat the whole survey, but looked only at the more common errors reported in the earlier one: no mention of randomization (in clinical trials); lack of description of statistical methods; failure to show variability; standard error given on samples of undefined or small ($n < 10$) size; statistical significance claimed without data; and values of probability given without data. Our findings were disappointing: 34 abstracts of 80 that needed statistics contained these simple errors. This proportion is not directly comparable with the 61 of 94 in the earlier survey because we have included fewer errors this time; Table 1 gives a better comparison, showing the number of errors, rather than the number of abstracts.

Table 1 Statistical errors, as absolute number of errors, and as percentage of abstracts needing statistics, identified in two surveys of precirculated Anaesthetic Research Society abstracts. Errors occurred in study design (1 and 2); presentation of variability (3 and 4); and presentation of probability (5 and 6). SEM = standard error of the mean. P = probability

	Abstracts 1990[1]		*Abstracts '95–'96*	
	Number	*As %*	*Number*	*As %*
Total abstracts	115	—	91	—
Needing statistics (n)	94	—	80	—
1 No mention of randomization	9	10	5	6
2 Lack of statistical description	29	31	17	21
3 No variability shown	5	5	5	6
4 SEM, no n or n<10	10	11	12	15
5 Significance claimed, no data	10	11	7	9
6 P given, no data	11	12	3	4
Total errors	74	—	49	—

There may have been some improvement. There were fewer abstracts in which significance was claimed or probabilities given without data to support them (although this error occurred in 10 of 80 abstracts), but overall there were a disappointing number of errors. This is especially disappointing because two of the faults, failure to show variability or to describe the statistics used, are mentioned in the guidelines on presentation of papers to the Anaesthetic Research Society.

Over the years, medical statisticians have been critical of medical researchers, and it is from the publications of one of those critics, D. G. Altman, that the original list of errors was drawn.[4-5] Error is the word that Altman uses and, with its implication of not keeping to recognized good practice, is more appropriate than other possible words, such as mistake or fault. A mistake implies a wrong choice or carelessness. A fault has implications of responsibility, which an error does not necessarily have. Anyone using statistics as an experimental tool should know how to use them — just as they should know how to use cell cultures, neuromuscular monitoring, liquid chromatography or whatever other experimental tool they use in their research. Error is also a useful word in this context because of the familiar expressions "error of omission" and "error of commission", and most of the errors from our repeated survey are errors of omission: it seems that investigators are not aware of the good practice required for statistical description.

The errors described by Altman, leaving aside for the moment misuse of the standard error of the mean, are not defendable. Randomization is necessary to reduce bias and because statistical theory is based on the idea of random sampling. Randomization is too important for it to be assumed; it should be stated explicitly. The statistical tests used must be described, to enable the reader to identify statistical errors and to determine whether the conclusions of a study are valid; in addition, and of fundamental importance, readers should not have to guess or presume what the investigators did. A mean or median with no indication of variability is simply uninterpretable. A statement of probability or of statistical significance without data is meaningless. Overall, if there are statistical errors, the conclusion of a study may be incorrect and misleading. There is no authority in statistics who would make allowances for these simple errors, so why do they occur in abstracts at the Anaesthetic Research Society? Why do they occur in spite of an explicit audit published in this journal asking that they should not occur and, for two of the errors, an explicit instruction in the guide to presenters? This is not just a domestic problem for the Anaesthetic Research Society, but a problem for the whole specialty. If the Obstetric Anaesthetists' Association speaks for its subspecialty, and the other subspecialty groups likewise, then the Anaesthetic Research Society speaks for research and research method, and is a window on that.

Abstracts cannot, of course, contain every detail of a study. One could argue that the investigators would not make these errors of omission in their full reports. That may be so; but abstracts are scientific presentations, even if not as polished as the final reports. They are presented to peers for scientific appraisal, which is less easy if detail is lacking. Investigators do not have the excuse that space is limited: 20 of the 34 abstracts had at least two lines spare; nine had more than five lines spare. There is a view that the abstracts of the Society should not be published in the *British Journal of Anaesthesia*. Whether or not they are published, the precirculated abstracts are still available to members of the Society. A future decision not to publish them would not affect the validity of future surveys, although if we take the statistical criticism seriously it throws doubt on the scientific validity of the abstracts.

The errors described in these surveys are basic. A survey by Avram and co-workers[5] was much more comprehensive. They were greatly concerned with the misuse of "elementary" hypothesis tests, making examples particularly of repeat testing and the use of parametrically based tests such as the *t* test on data suitable only for non-parametric analysis. They considered their study used "only simple criteria"; our survey is even simpler. Nor have we considered another important statistical problem: studies that are too small to detect important differences[6] — so-called beta, or Type II, error.

There are three broad questions. Why are these errors made? Do they matter? How can statistical practice be improved? The first is easy to answer. Anaesthetists in general are not comfortable with statistics. Candidates for the Fellowship examinations approach cardiorespiratory tutorials with enthusiasm; they approach statistics tutorials with dread and resignation. Yet the amount of statistics needed for the examinations, and indeed for much of the research that those candidates may later do, is small. The necessary degree of understanding is far less than in cardiorespiratory physiology.

There is published evidence of anaesthetists' dislike of statistics. In a survey reported by Burnstein and colleagues,[7] a quarter of respondents in the unprompted section thought knowledge of statistics was irrelevant to the practice of anaesthesia. Half the respondents felt that the only knowledge needed was of the various statistical tests, implying that a "recipe-book" approach is all that is necessary. Almost half the respondents felt unable to give a tutorial on statistics. We suspect that anaesthetists actively involved in research would give different answers, but our surveys, and the lack of statistical insight of many of the presenters at the Anaesthetic Research Society, suggest that statistics is still not taken seriously. Presenters are often trainee anaesthetists, but while the error may be theirs, most of the responsibility lies elsewhere, with their supervisors.

Do the errors matter? We would not be writing this editorial if we did not think so, and there are enough published commentaries on medical statistics to suggest that there are many others who think likewise. So how can statistics be improved? We concluded our earlier survey by suggesting that by using statistical checklists, and with the help of local statisticians, the Anaesthetic Research Society had the opportunity to play its part in improving the general standard of the reporting of medical research. In the intervening 5 years that has not happened. Statistical checklists and local statisticians are not as helpful as a proper understanding of statistical principles, which boils down really to a proper understanding of probability and of the spread of data. These principles underlie the ideas of taking samples from a population and of the valid estimation of measures from those samples. No knowledge of the mechanics of any statistical test is needed, as long as there is some knowledge of which test is appropriate — for which a statistician is helpful; and of what the result means — which is where the understanding is essential. A researcher with a proper understanding of statistics would not present a mean without variability, or fail to state the statistical test used.

A researcher with a proper understanding of statistics would also know when the standard error of the mean is appropriate.[8] The misuse of the standard error, especially its use for small samples, is not as simple an error as failing to show variability, but it is a good indication of statistical understanding. The standard error does not show the spread of data; the standard deviation does that. The standard error enables a calculation of confidence in the mean, and it is this confidence interval that is the statistic with real meaning. A 95% confidence interval of 10 mm Hg around a mean arterial pressure of 125 mm Hg implies 95% probability that the true mean arterial pressure of the population from which the sample was drawn lies between 115 and 135 mm Hg. For large samples, the 95% confidence interval is twice the standard error. For smaller samples, not only is the standard error larger, but the 95% confidence interval becomes progressively more than twice the standard error. The size of sample below which the standard error (and, by implication, the confidence interval) becomes less useful is a matter of convention, in just the same way that the cut-off of $P < 0.05$ is convention. It just seems a matter of common sense that it is not wise to try to fix the mean of the population from a sample of five or six.

Are we right to criticise research in anaesthesia and bring these criticisms to possibly wider attention, especially when anaesthesia research is under enough strain?[9] We have not compared anaesthesia with other specialties, nor anaesthesia in Britain with that in other countries, though there is no reason to suppose anaesthesia, or Britain, is any better or worse than other specialties or countries. When we complete the clinical audit cycle in our hospitals we compare now with then, rather than compare here with elsewhere, and that is what our surveys have done. There is little change. Whatever damage publication of our findings might do now, it will be worse in the future if nothing happens. If other specialties wish to take us to task, then they must do so on evidence of better statistical practice in their specialties — and comparisons of our surveys with their published work will not do that.

Since Altman complained that "The general standard of statistics in medical journals is poor"[4] there have been great improvements. In that time many journals, of which the *British Journal of Anaesthesia* is one, have introduced statistical checklists. Otherwise-accepted manuscripts are now far more likely to be sent to a statistician or at least to someone with a statistical interest. The system is much improved, but our survey, and experience at research meetings, such as those of the Anaesthetic Research Society, suggests that better statistical knowledge among researchers would ease the workload of referees. It is a shame when discussion of an interesting project becomes bogged down because of the misuse of simple statistics.

More statistical emphasis in the anaesthesia examinations is not the answer. Candidates soon forget. Perhaps the emphasis should change from statistics in the narrow sense to the wider aspects of good study design. All practising clinicians must have some knowledge of this to enable any critical appraisal of what is published. But it is those actively involved in research who need to have an immediate feel for statistics: supervisors have a responsibility to teach their researchers, or to ensure there is someone who can do so; researchers must realize the importance of statistics. Researchers also have a responsibility: to ask for teaching in statistics relevant to their projects. We need to get away from the all-too-common feeling among researchers that statistics is just an awkward encumbrance to the real business of research, a feeling often paradoxically coupled with an undue reliance on the magic figure of a probability of less than 0.05.

Altman and many others have criticised medical journals. We can take some comfort that one of the errors that they and we have looked at — the misuse of standard error — is rife in one of the foremost scientific journals, *Nature*. *Nature* publishes little of relevance to anaesthesia but this is changing with the recent interest in the possibility that specific protein sites are involved in the mode of action of anaesthetics. In their paper, Mihic and co-workers[10] show data as "mean ± s.e.m. of between 4 and 14 oocytes". There are five other papers in the same issue of *Nature* in which the standard error is given on between five and eight observations, and one in which the number of observations is not given at all. Altman complained that "the presentation of variability in medical journals is a shambles",[11] but many figure legends in *Nature* have undefined error bars, and it takes careful reading of the text to determine what they do represent. In one figure, means and standard deviations were given for sets of three observations. To assume a knowledge of a distribution from three measurements is nonsense. On a more trivial level, it takes more ink to show the means and error bars than it would to show all the actual measurements. As Altman wrote of medical journals: "some practices are now considered obligatory purely because they are widely used and accepted, not because they are particularly informative."[11] Our specialty's response to this should not be that what *Nature* does is good enough for us, but that even a journal with the highest scientific reputation can get it wrong, and in some ways we can better them. The widespread impression that clinical research is less sound, statistically and otherwise, than basic scientific research may be false: Muers wrote of respiratory physiology[12] that whereas "therapeutics needs tens of thousands of patients, valid and persuasive physiological evidence continues to be drawn from studies of a mere one or two subjects."

The statistical sensibility of anaesthesia journals is higher than it used to be, but it needs to filter down to those doing the research in anaesthesia. There is no instant solution, but those who have this sensibility must take every opportunity to impart it to those who do not. This means that they must not be afraid to speak statistically whenever they can, and researchers must expect to be questioned on their basic understanding of statistics if that understanding appears to be shaky.

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CLINICAL INVESTIGATIONS

Do the pharmacokinetics of vecuronium change during prolonged administration in critically ill patients?

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Summary

Neuromuscular blocking drugs may be administered over several days to patients in the intensive care unit (ICU), but their pharmacokinetics have been studied at only one point in time, or assumed to be constant throughout the period of administration. We sought to determine if, in individual patients, the pharmacokinetics of vecuronium changed over the course of its administration in the ICU. In six critically ill patients, we measured plasma vecuronium concentrations during two periods: first, during initial administration of vecuronium and second, after its administration continuously for 3–6 days. A pharmacokinetic model was fitted to these plasma concentration data, and its parameters permitted to vary between the periods to determine if they had altered. Individual clearance values during the study ranged from 1.4 to 4.4 ml kg^{-1} min^{-1}. During prolonged administration, vecuronium clearance increased in three and decreased in two patients. This change ranged from a 61% decrease to a 58% increase, and was not linked to any clinical factor. The steady-state volume of distribution (range 368–1765 ml kg^{-1}; median 494 ml kg^{-1}) did not change in any patient during the study. The change in clearance of vecuronium during its prolonged administration in critically ill patients suggests that future studies of neuromuscular blocking drugs in the ICU should take account of their changing pharmacokinetics over the course of administration. (*Br. J. Anaesth.* 1998; **80**: 715–719)

Keywords: intensive care vecuronium, neuromuscular block vecuronium; pharmacokinetics vecuronium

The administration of neuromuscular blocking drugs is a common practice in the intensive care unit (ICU), where these drugs may be given for days or weeks.[1-3] Studies of the pharmacokinetics of neuromuscular blocking drugs in the ICU have been performed at only a single time during drug administration[4 5] or, if the study was conducted over several days, it was assumed that the pharmacokinetics were constant during the period of study.[6] Because neuromuscular blocking drugs are often given for several days, during which time the physiological status of the patients may alter, the pharmacokinetics of the drugs may also change, and an estimate of pharmacokinetics at one point in time may not be accurate at a later time. Vecuronium has been used commonly, and for prolonged periods, in the ICU.[4 7 8] In the present study we determined the pharmacokinetics of vecuronium in patients in the ICU, and investigated whether the pharmacokinetics in individual patients changed during prolonged administration of the drug. If the pharmacokinetics of vecuronium change during prolonged administration, the potential for changing pharmacokinetics should be taken into account in future studies of other neuromuscular blocking drugs in the ICU.

Patients and methods

The study was approved by the Committee of Human Research of the University of California at San Francisco. After obtaining written informed consent from each patient's next of kin and primary ICU physician, we consecutively studied six critically ill patients (three males, three females) aged 22–86 yr. Patients receiving assisted ventilation for adult respiratory distress syndrome (ARDS) were screened for possible enrolment in the study if the attending ICU physician decided that neuromuscular block was clinically indicated. Patients with a history of neuromuscular disease, renal failure requiring haemodialysis, or administration of a neuromuscular blocking drug in the 24 h before the start of the study were excluded.

PHARMACOKINETIC STUDY

In all patients vecuronium was administered i.v. at a rate of 6 μg kg^{-1} min^{-1} until complete neuromuscular block was induced (approximately 10 min). Arterial blood was sampled before and at 2, 4, 6, 8, 10, 15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300 and 360 min after the beginning of the infusion.

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Table 1 Patient characteristics, plasma creatinine, total bilirubin, and liver function grade during initial administration of vecuronium (I) and after stopping its administration (II) in critically ill patients. *Liver function was graded in four classes: 0 = normal liver function tests; 1 = increased plasma aspartate aminotransferase (AST) and alkaline phosphatase (ALK-P) levels without increased bilirubin concentration or prothrombin time; 2 = increased plasma AST, ALK-P and bilirubin concentrations without increased prothrombin time; 3 = increased prothrombin time caused by altered liver function

				Weight (kg)		Creatinine (μmol l^{-1})		Bilirubin (μmol l^{-1})		Liver function*	
Patient	Primary pathology	Sex	Age (yr)	I	II	I	II	I	II	I	II
1	Sepsis	M	58	58	56	88	115	0.7	0.9	1	1
2	Liver failure	F	32	61	60	150	168	31	41	3	3
3	Unknown	F	39	69	65	80	71	0.3	0.1	1	1
4	Sepsis	M	86	64	67	159	248	0.6	0.6	0	0
5	Pneumonia	M	27	67	74	106	124	10.4	12.5	2	3
6	Sepsis	F	22	64	67	80	71	20	18.1	2	2

Table 2 Reasons for mechanical ventilation and sedative drugs used

Patient	Primary pathology	Aetiology of respiratory failure	Sedation and analgesia
1	Non-Hodgkin's lymphoma	Pneumocystis pneumonia; systemic candidiasis	Midazolam, lorazepam, morphine
2	Alcoholic cirrhosis and encephalopathy	Aspiration pneumonia	Lorazepam, morphine
3	Postoperative urinary tract infection	Enterococcal sepsis	Midazolam, morphine
4	Repair of abdominal aortic aneurysm	Aspiration pneumonia	Midazolam, lorazepam, fentanyl
5	Testicular cancer and pancytopenia	Sepsis of unknown aetiology	Midazolam, morphine
6	Malignant histiocytosis and pancytopenia	Staphylococcal sepsis	Midazolam, pethidine

Subsequently, vecuronium was given by continuous infusion or frequent intermittent boluses according to clinical requirements. This method of administration continued until the patient's clinical status suggested that vecuronium therapy might be discontinued within the next 12 h. At this time, in all patients, vecuronium administration was changed to a continuous infusion at an hourly rate equal to the average hourly requirement over the preceding 24 h. This infusion was continued unchanged for 12 h, then discontinued. Three arterial blood samples were drawn during the 60 min just before discontinuing the vecuronium infusion and at intervals for up to 8 h after stopping the infusion. All samples were placed in ice and processed within 1 h.

Plasma concentrations of vecuronium were determined by a capillary gas chromatographic assay specific for vecuronium, with a coefficient of variation of 15% at concentrations of 15 ng ml^{-1} and a sensitivity of 10 ng ml^{-1}.[9] If, after withdrawal of vecuronium, the patients did not tolerate mechanical ventilation, atracurium was given during the period of blood sampling because it does not interfere with the vecuronium assay.

Data from each subject were analysed separately but all data from each subject were analysed together using nonlinear mixed-effects modelling (NONMEM).[10] Subjects were assumed to have reached a steady state before discontinuation of the final infusion. Basic parameters of the models were clearance (*Cl*), intercompartmental clearances (Q_1 and Q_2), and volumes of distribution V_1, V_2 and V_3. Volume of distribution at steady state (V^{ss}) was equal to $V_1 + V_2 + V_3$. First two- and three-compartment mamillary models were fitted to the data from each subject. The three-compartment model was used subsequently only if it could be statistically justified. Next, additional (change) parameters were introduced, each permitting one basic parameter (*Cl*, V_1 etc.) to vary from the first to the second infusion. These change parameters were accepted into the model only if they statistically and visually improved the fit of the model to the data. When all justified parameters had been introduced, the necessity for each one was tested by removing it and obtaining fresh parameter estimates. The necessity for a change parameter was used to evaluate whether or not a basic parameter had altered, and the magnitude of the change in the basic parameter was determined from the value of the change parameter.

Statistical justification for the use of a three-compartment rather than a two-compartment model and for inclusion of a new parameter in the model was a decrease of 9.2 in the NONMEM objective function ($P < 0.01$).[10]

Table 3 Details of NONMEM pharmacokinetic analysis. *In the basic model, volumes of distribution and clearance are assumed to be the same throughout the administration of vecuronium. In the other models, volumes of distribution, or clearance or both are allowed to vary between the time of initial administration and the end of administration of vecuronium, several days later. A decrease in the objective function of 9.2 denotes a significant improvement over a simpler model (P<0 01). Bold type: values for the optimal model

Patient	1	2	3	4	5	6
Vecuronium administration						
Days of administration	5	4	6	4	3	4
Total dose (mg)	331	115	342	180	135	212
Value of objective function*						
Basic model	347.7	277 5	161.0	216.1	261.6	**219.8**
Volume allowed to vary	339.0	263.3	161.0	211.0	261.2	219 7
Clearance allowed to vary	**302.2**	**231.8**	**151.7**	**195.8**	**246.3**	218.6
Volume and clearance allowed to vary	299.6	231.0	151.2	191.1	245.9	N/A

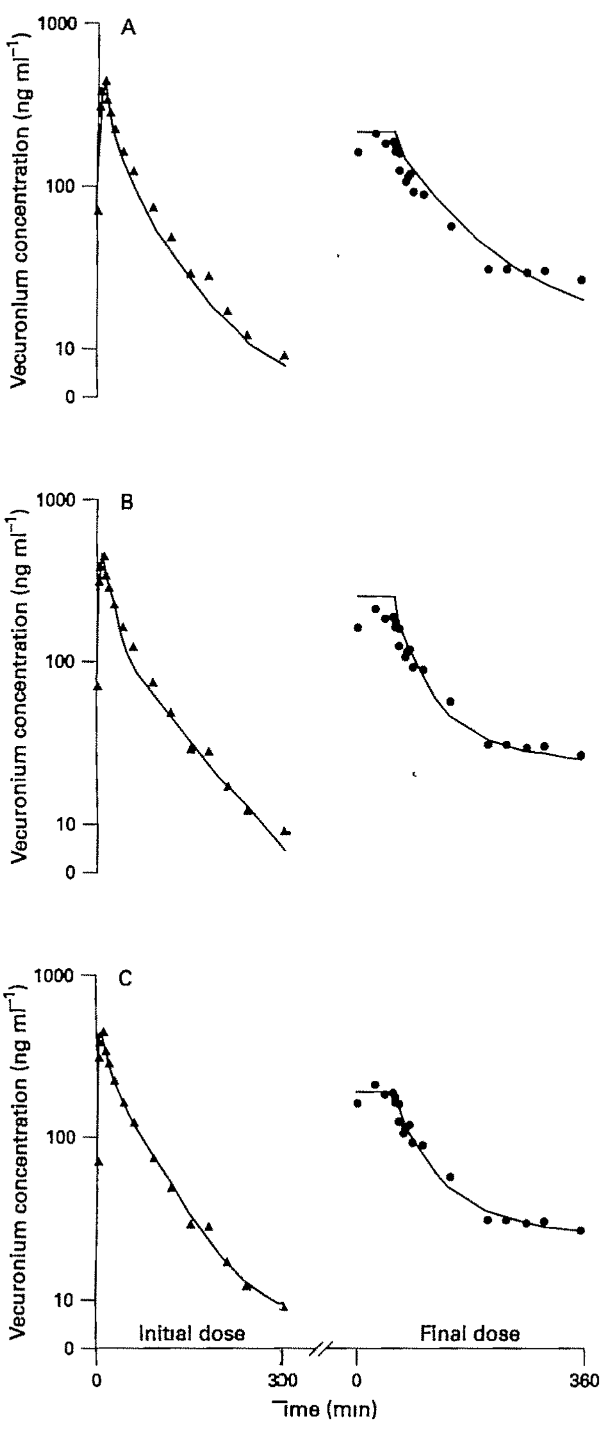

Figure 1 Plasma concentration *vs* time curves for patient 2. Symbols represent actual plasma concentrations. The initial and final doses are separated by a period of 4 days (represented by //). (A) Fitted curve with clearance and volumes of distribution assumed to be constant throughout the period of vecuronium administration. (B) Fitted curve with clearance assumed to be constant and volumes of distribution allowed to vary between the initial and final administration vecuronium; there is no visual or statistical improvement over previous fit. (C) Fitted curve with volumes of distribution assumed to be constant and clearance allowed to vary between the initial and final administration vecuronium; this final fit is visually and statistically ($P < 0.01$) superior to the previous two fits.

Table 4 Individual pharmacokinetic values during initial administration of vecuronium (I) and after its administration for several days (II) in critically ill patients. *Mean residence time was calculated as volume of distribution/plasma clearance

Patient	Steady-state volume of distribution (ml kg^{-1})	Plasma clearance (ml kg^{-1} min^{-1})		Mean residence time* (min)	
		I	II	I	II
1	436	3.6	1.4	123	304
2	836	1.9	3.0	452	277
3	1765	3.0	4.4	586	397
4	368	2.5	2.1	146	174
5	496	1.8	2.2	273	224
6	492	3.0	3.0	166	166
Median	494	2.8	2.6	219	251

CLINICAL DATA

Renal and liver function tests were performed for all patients on the first and final days of the study. Renal function was assessed using plasma creatinine concentrations. Plasma concentrations of total bilirubin, aspartate aminotransferase (AST) and alkaline phosphatase (ALK-P) were measured. If the results suggested an abnormality, prothrombin time was also measured. Liver function was graded in four classes: 0 = normal liver function tests; 1 = increased plasma AST and ALK-P levels without increased bilirubin concentration or prothrombin time; 2 = increased plasma AST, ALK-P and bilirubin concentrations without increased prothrombin time; and 3 = increased prothrombin time because of altered liver function. The administration of vasoactive drugs, and of any drugs that might alter the pharmacology of vecuronium, was recorded.

Results

CLINICAL DATA

Patient characteristics, renal and hepatic function are detailed in table 1. For all but one patient (patient 4), plasma creatinine concentration changed less than 30 μmol l^{-1} during the study period; in patient 4, the plasma creatinine concentration increased from 159 to 248 μmol l^{-1}. Liver function changed little in any patient during the study, and only for patient 5 did the grade change. In this patient, prothrombin time increased from a normal value of 13.1 s to a marginally elevated value of 14.2 s, resulting in his score changing from 2 to 3.

In all patients, mechanical ventilation was instituted for respiratory failure. Vecuronium was administered to enable the patients to tolerate mechanical ventilation, after appropriate sedation had been given. The patients' lungs were ventilated to achieve normocapnia. The patients' underlying pathology and the aetiology of their respiratory failure are shown in table 2.

Only one patient (patient 2) required inotropic support, and this was during the late phase only, using dopamine at an average rate of 6 μg kg^{-1} min^{-1}; patients 4 and 6 received dopamine in renal doses of 1.6–3.2 μg kg^{-1} min^{-1}. All patients except patient 2 received an aminoglycoside antibiotic during the course of vecuronium administration. Patients 1, 4 and 5 received frusemide during the early, but not the late, phase of the study. Patients 1, 5 and 6 received hydrocortisone throughout the study. Patient 6 received phenytoin throughout the study.

PHARMACOKINETIC STUDY

For all patients, the three-compartment model was superior. Allowing the V^{ss} to vary between early and late phases did not improve the fit in any patient (table 3, figure 1). In contrast, for five of the six patients, there was a significant improvement in fit when *Cl* was allowed to change from early to late phases (table 3, figure 1). Allowing the intercompartmental clearances to vary from early to late phases did not improve the fit in any patient.

The values of the pharmacokinetic variables are given in table 4. V^{ss} was calculated by summing the volumes of each of the three compartments, and mean residence time was calculated as V^{ss}/Cl. V^{ss} (range 368–1765 ml kg^{-1}; median 494 ml kg^{-1}) did not change in any patient during the course of vecuronium administration. In contrast, the clearance of vecuronium (range 1.4–4.4 ml kg^{-1} min^{-1}) increased in three and decreased in two patients.

Only one patient (patient 4) had a significant deterioration in renal function, and this was accompanied by a small decrease in clearance from 2.5 to 2.1 ml kg^{-1} min^{-1}. In patient 5 liver function deteriorated slightly, but clearance increased from 1.8 to 2.2 ml kg^{-1} min^{-1}.

Discussion

We found that the clearance of vecuronium changed in five of six patients over the course of vecuronium administration. There was no consistent pattern to this change; clearance increased in three patients and decreased in two. There are several potential reasons why clearance changed; among them are alterations in organ function, and the administration of drugs that might influence the biodisposition of vecuronium.

The largest change in clearance occurred in patient 1, in whom it decreased from 3.6 to 1.4 ml kg^{-1} min^{-1}. This was accompanied by an increase in creatinine from 88 to 115 μmol l^{-1} and no change in liver function. Even if renal function had deteriorated to a greater extent than was reflected by the relatively small change in creatinine, we consider it unlikely that the deterioration in renal function produced the decrease in clearance, as even in anephric patients vecuronium clearance may not change.[11] The haemodynamic status of this patient actually improved during the study (mean arterial pressure of 86 and 117 mm Hg during early and late phases respectively), without the administration of vasoactive drugs. We could identify no other factors in this patient's course that would account for the decrease in clearance of vecuronium.

Because vecuronium is eliminated by both kidney and liver we would have expected changes in function of these organs to have been reflected in changes in clearance.[12 13] However, in patient 4, who had significant deterioration in renal function, clearance decreased only slightly (2.5 to 2.1 ml kg^{-1}min^{-1}), and in patient 5 whose liver function deteriorated slightly, clearance actually increased from 1.8 to 2.2 ml kg^{-1} min^{-1}. The reason that we saw little relationship between organ function and clearance may be that the changes in organ function were relatively small and, additionally, other factors were influencing clearance, such as the administration of diuretics. Patients 1, 4 and 5 received frusemide during the early, but not the late, phase of the study and we could speculate that the resultant diuresis may have artificially increased vecuronium clearance in the early phase. The only data on the effect of an induced diuresis on the clearance of a neuromuscular blocking drug relate to mannitol, which had no influence on the clearance of *d*-tubocurarine.[14] In the absence of data, we cannot draw any conclusions about the possible interaction between frusemide and vecuronium clearance.

Patient 6 was receiving phenytoin, which significantly alters the neuromuscular response to vecuronium.[15] Vecuronium clearance in this patient did not change during the study, however, possibly because she had been receiving long-term phenytoin and any effect of the drug on vecuronium clearance would have been present at the start of the study.

Patients were receiving a variety of other drugs, for example aminoglycoside antibiotics and hydrocortisone, that interact with vecuronium and alter its pharmacodynamics, but have no known effect on its pharmacokinetics. Because patients in the ICU receive many drugs, interactions might occur that affect the pharmacokinetics of vecuronium, but as there are no data available we cannot speculate further on such possible interactions.

During the pharmacokinetic analysis, we assumed linearity, namely that plasma concentrations of vecuronium were proportional to the dose administered and that clearance would not vary with vecuronium concentration. This basic assumption underlies the pharmacokinetic modelling of nondepolarizing neuromuscular blocking drugs, and is supported by experimental evidence.[16] In a carefully controlled study, Wright and colleagues demonstrated that the pharmacokinetics of vecuronium were linear over an almost three-fold dose range.[16] In our study, the plasma concentrations of vecuronium were within the range of those studied by Wright and colleagues,[16] but our experimental conditions were different. Wright and colleagues studied healthy volunteers and vecuronium was administered for only brief periods; our subjects were critically ill and vecuronium was administered over several days. Thus, although we consider it unlikely that nonlinearity developed over the course of our study, we cannot rule out the possibility.

As vecuronium clearance could decrease or increase with time in an individual patient, the mean values for the patients as a group would not have differed between the early and late phases of the study. For this reason, we estimated the clearance and its change over time for subjects as individuals, and not as a group. Because patients in the ICU are so heterogeneous with regard to their pathophysiological state, expressing their characteristics as a mean value for a group is potentially misleading; in this study it would have suggested a stability in clearance which did not exist.

We found no change in the V^{ss} of vecuronium during the study, but the interindividual values (368–1765 ml kg^{-1}) varied over a four-fold range; the mean value was 732 and the standard deviation 531 ml kg^{-1}, so the coefficient of variation was approximately 70%. These values for mean and coefficient of variation are similar to those from an earlier vecuronium ICU study (1100 ml kg^{-1}, 55%).[4] This apparent large variability in V^{ss} in patients in the ICU probably results from the heterogeneous nature of these patients, with regard in particular to their underlying disease processes and level of organ function. As we studied only six patients, we cannot preclude the possibility that, in other patients, the V^{ss} for vecuronium might have changed over the course of the drug's administration.

The mean value for V^{ss}, 732 ml kg^{-1}, is greater than the range (180–510 ml kg^{-1}) reported after acute administration in the operating theatre in patients with normal or with impaired renal or hepatic function.[17] This apparently large estimate for V^{ss} probably is a result of the chronic administration of vecuronium, and consequently revelation of its distribution into a large peripheral compartment with low blood flow. This finding is consistent with the results of Matteo and colleagues, who, because they measured plasma concentrations for 96 h, estimated the volume of distribution of *d*-tubocurarine as 3.4 l kg^{-1}.[14]

This hypothesis of a large peripheral compartment with low blood flow is supported by the work of Waser and colleagues.[18] Using whole-body autoradiography in rats, they demonstrated that vecuronium is distributed widely, including into tissues with low blood flow, such as connective tissue. After acute administration of vecuronium, and with sampling periods of 6 h, the amount of drug in this peripheral compartment would be minimal, would not be revealed in the plasma concentration *vs* time curve, and hence would not influence the calculation of pharmacokinetic variables. However, with continued administration, progressively greater amounts of vecuronium would accumulate in the slowly equilibrating peripheral compartment. After discontinuation of vecuronium, distribution of the drug from this slow peripheral compartment into the plasma would significantly influence the decay profile of the plasma concentration *vs* time curve, and the larger V^{ss} would be revealed.

Normal clinical practice in our ICU dictated the regimen for administration of vecuronium over the course of the study. This resulted in continuous infusion, or regular and frequent bolus doses of vecuronium. The dose of vecuronium was increased until the patients tolerated mechanical ventilation, and remained unchanged thereafter. This regimen allowed us to model the pharmacokinetics of vecuronium using the assumption of steady-state, during the period between the early and late phases of the study.[10]

Vecuronium has a 3-desacetyl metabolite that has significant neuromuscular blocking potency.[19] It was not the aim of this study to investigate the metabolite, but rather to determine whether the pharmacokinetics of the parent compound, vecuronium, changed with time. Because of our results with vecuronium, it is a reasonable assumption that the pharmacokinetics of its metabolite also change with time.

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Dose-response curve and time-course of effect of vecuronium in male and female patients

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Summary

To determine the differences between men and women in the dose-response curve and the time-course of effect of vecuronium, we studied 60 adult patients (30 male and 30 female), ASA I, age 18–51 yr, undergoing elective plastic surgery. Anaesthesia was maintained with nitrous oxide 60% in oxygen; thiopentone and incremental doses of fentanyl were given as required. Neuromuscular function was assessed mechanomyographically using the train-of-four (TOF) stimulation at the wrist every 12 s. The percentage depression of T_1 was used as the study variable. The dose-response relationship of vecuronium was determined by a cumulative dose-response technique. The dose-response curve in men was shifted in a parallel fashion to the right, indicating a decrease in the sensitivity to vecuronium-induced neuromuscular block, compared with women. The ED_{50}, ED_{90} and ED_{95} of vecuronium were 23.9 (4.7), 45.4 (11.2) and 55.7 (14.3) $\mu g\ kg^{-1}$ in men and 18.4 (3.7), 33.5 (7.8) and 39.8 (9.6) $\mu g\ kg^{-1}$ in women respectively. There were statistically significant differences in these values between the two groups ($P<0.01$ in each instance). After a total dose of vecuronium 80 $\mu g\ kg^{-1}$, neuromuscular block was significantly longer in women than in men. The duration of peak effect, clinical duration, and the total duration were 18.7 (7.1), 26.6 (8.8) and 50.6 (16.0) min respectively in men and 26.0 (7.2), 37.1 (11.2) and 65.9 (20.7) min in women. They differed significantly between men and women ($P<0.005$ in each case). (*Br. J. Anaesth.* 1998; **80**: 720–724)

Keywords: neuromuscular block vecuronium; pharmacodynamics vecuronium; gender

In recent years, possible factors influencing the pharmacokinetics and pharmacodynamics of vecuronium have been studied extensively. It is well documented that increasing age,[1 2] hepatic insufficiency,[3] respiratory acidosis,[4] hypothermia,[5] obesity,[6] inhalation anaesthetic agents,[7–9] other neuromuscular blocking drugs,[10 11] aminoglycoside antibiotics,[7] and myasthenia gravis[12] make patients more sensitive to vecuronium, but there is controversy about the effect of gender on neuromuscular block produced by vecuronium. Semple and colleagues[13] reported that women required 22% less vecuronium than men to achieve the same degree of neuromuscular block. Houghton, Aun and Oh[14] showed that the condition of male patients was significantly less satisfactory than that of female patients when the trachea was intubated 60 s after administration of vecuronium 100 $\mu g\ kg^{-1}$. However, Gramstad and Lilleaasen[15] found no such difference. In addition, it is not known whether there is any difference in the time-course of action of vecuronium in men and women. It was the purpose of the present study to evaluate the influence of gender on the dose response and on the pharmacodynamics of vecuronium in healthy adult patients under nitrous oxide–oxygen–fentanyl anaesthesia.

Patients and methods

After obtaining ethics committee approval and written informed consent, we studied 60 healthy adult patients (30 male and 30 female), ASA I, aged 18–51 yr and weighing 47–84 kg, who were undergoing elective plastic surgery expected to require general anaesthesia for >120 min. All the patients were Chinese of the Han race. Patients were excluded if they had cardiac, pulmonary, renal, hepatic, neurological, psychiatric, muscular, inflammatory, malignant or endocrine disease, as were pregnant women, patients undergoing major reconstructive surgery for burns, and patients with recent exposure (within 72 h) to medications known to interfere with neuromuscular transmission. Those with a body weight more than 10% above ideal were not studied. Ideal body weight was defined as follows: for males, 110 lb+5 lb $inch^{-1}$ above 5 ft height; for females, 100 lb+5 lb $inch^{-1}$ above 5 ft height.[6]

After an overnight fast, patients were premedicated with diazepam 0.2 mg kg^{-1}, meperidine 1 mg kg^{-1} and atropine 0.01 mg kg^{-1} i.m. 1 h before anaesthesia. Anaesthesia was induced with thiopentone 4–6 mg kg^{-1} and fentanyl 2–4 $\mu g\ kg^{-1}$. After topical anaesthesia with 2% lidocaine, the trachea was intubated without the aid of a neuromuscular blocking drug. Anaesthesia was maintained with nitrous oxide and oxygen in the ratio 3:2 (total flow 5 l min^{-1}), and intermittent bolus doses of thiopentone. For analgesia, bolus doses of fentanyl 2 $\mu g\ kg^{-1}$ were given if there were clinical signs of inadequate analgesia (heart rate or

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Table 1 Patient characteristics. Values are mean (SD) (range)

	Male (n=30)	Female (n=30)
Age (yr)	28.3 (8.1) (18–49)	29.5 (7.7) (20–51)
Weight (kg)	58.6 (10.8) (47–84)	57.2 (9.2) (48–75)
Height (cm)	165.4 (8.7) (160–180)	163.7 (9.2) (158–176)
Duration of surgery (h)	3.6 (1.1) (2.3–6.2)	3.8 (1.3) (2.8–6.1)
Temperature (°C)	36.5 (0.4) (36.5–37)	36.4 (0.4) (36.4–37)
Haemoglobin (g dl^{-1})	14.8 (1.5) (12.5–16.7)	14.7 (1.5) (13–16.6)

mean arterial pressure >20% above baseline values). Ventilation was controlled to maintain $P\text{E}'_{CO_2}$ at 4–5 kPa.

Inspired and end-tidal concentrations of oxygen, carbon dioxide and nitrous oxide were measured continuously and displayed digitally with an anaesthetic gas analyser (Capnomac Ultima, Datex). A cannula was placed in the radial or femoral artery for sampling. Arterial pH, Pa_{O_2}, Pa_{CO_2}, K^+, Na^+, Cl^- and ionized calcium were determined with a blood-gas-electrolyte analyser Model-5 (Nova Biomedical Company, Hoboken, USA) before and during surgery. Total plasma protein and albumin were measured with an automatic biochemical analyser Type-550 (Corning Medical, Oberlin, OH, USA). Thenar skin temperature was monitored using a thermocouple placed on the dorsum of the hand, from which the response to ulnar nerve stimulation was recorded. Skin temperature over the thenar muscles was maintained above 32°C throughout the study period by wrapping the arm in cotton-wool.

Neuromuscular function was assessed using mechanomyography of the thenar muscles. The ulnar nerve was stimulated at the wrist with a nerve stimulator in train-of-four (TOF) mode (Myotest MK, Biometer, Odense, Denmark) through surface electrodes. Supramaximal, square-wave impulses of 0.2 ms duration at 2 Hz were administered every 12 s. The hand and forearm were immobilized in supination and abduction on a splint, and the fingers were strapped in extension. Evoked muscle contraction of the adductor pollicis was quantified isometrically by a force displacement transducer, amplified, and recorded continuously on a polygraph. The first response (T_1) of the TOF stimulus was used as the parameter for pharmacodynamic measurements. The dose-response relationship for vecuronium in the two groups was determined using a cumulative dose-response technique according to Donlon and colleagues.[16] A total dose of vecuronium 40 μg kg^{-1} was given in four doses of 10 μg kg^{-1}. Each dose of vecuronium was injected as an i.v. bolus over <5 s into a rapidly running i.v. infusion. Five min were allowed for stabilization of the response to TOF stimulation before giving the first dose of vecuronium. The mean of 10 T_1 responses, immediately preceding the first administration of vecuronium, was accepted as the control with which all subsequent T_1 responses were compared. Each dose increment was given (at times t1, t2 and t3, respectively) only after the effect of the previous dose had reached a stable response, defined as three equal (±1%) consecutive T_1 responses, or when 5 min had passed with no decrease in T_1 from control. If 90% or more T_1 depression was achieved after the second incremental dose, the third incremental dose was not used.

The individual dose-response relationship was examined by least squares linear regression of the logarithm of each dose against a probit transformation of the depression of T_1, from which the doses required for 50%, 90%, and 95% T_1 depression (ED_{50}, ED_{90} and ED_{95}, respectively) were calculated. The regression lines were tested to determine if they deviated from parallelism.[17] If they did not, ED_{50}, and ED_{95} values were compared between the groups. Parallelism was tested using one-way analysis of variance followed by the Student–Newman–Keuls multiple range test of the steepness coefficients of the regression lines (α).

When maximal depression of the T_1 response had occurred after the final increment, additional doses of vecuronium 40 μg kg^{-1} or 50 μg kg^{-1} (total dose 80 μg kg^{-1}) were given. If the resulting depression of the T_1 was 100%, duration of peak effect (time from injection of total dose of vecuronium 80 μg kg^{-1} to recovery of T_1 response to 5%), clinical duration (time from injection to 25% recovery), total duration (time from injection to 90% recovery), and recovery index (time from 25% to 75% recovery) were estimated.

All data were stored on disk and analysed with POMS statistical software Version 2.1 (Shanghai Scientific and Technical Publishers, Shanghai, People's Republic of China). An analysis of covariance was used to compare the dose-response curves of the two groups. The possible effects of age, weight, and gender on the peak depression of the T_1 response to a given dose of vecuronium were analysed by multiple linear regression; the significance of added regressors was tested using the F test. Statistical comparisons of other data between and within groups were carried out using the unpaired and paired Student's *t* test, respectively. Data are expressed as mean (SD). $P<0.05$ was considered significant.

Results

The patient characteristics of the two groups were comparable (table 1). All patients had stable haemodynamics and were normothermic throughout the study. There were no significant differences between male and female patients in arterial blood gas data or plasma electrolytes before and during surgery. However, the concentrations of total plasma protein and albumin in the women were decreased by 8–10% and 11–16% respectively compared with those in the men ($P<0.01$) (table 2).

The third incremental dose was not used in four women and two men because 90% or more of T_1 depression was achieved after the second incremental dose. The times of administration of the first (t1), second (t2), and third (t3) increments were 4.7 (1.3) min, 9.5 (2.1) min, and 12.6 (3.1) min respectively in the men, and 4.6 (1.2) min, 9.4 (2.5) min, and 12.1 (2.8) min in the women. There was no statistically significant difference between the two groups ($P>0.05$). When all the patients were considered together, the patients' age and weight were not significantly correlated with the peak depression of

Table 2 Arterial blood gas data, electrolyte concentrations, total plasma protein (TPP) and albumin before and during surgery in the male and female patients. Values are means (SD). ⁺Calcium=ionized calcium. *$P<0.01$, compared with preoperative value; †$P<0.01$, compared with male patients

	Male (n=30)		Female (n=30)	
	Before surgery	During surgery	Before surgery	During surgery
pHa	7.40 (0.03)	7.44 (0.04)	7.41 (0.02)	7.43 (0.03)
Pa_{CO_2} (kPa)	5.3 (0.2)	4.5 (0.3)*	5.4 (0.2)	4.6 (0.2)*
Pa_{O_2} (kPa)	12.6 (0.8)	19.2 (1.2)*	12.7 (1.0)	19.6 (1.2)*
K^+ (mmol l^{-1})	4.3 (0.3)	4.2 (0.2)	4.2 (0.2)	4.0 (0.2)
Na^+ (mmol l^{-1})	144.3 (3.5)	145.8 (2.8)	143.7 (3.2)	145.2 (2.8)
Cl^- (mmol l^{-1})	105.3 (1.7)	108.4 (1.3)	104.5 (1.3)	105.8 (2.0)
⁺Calcium (mmol l^{-1})	1.18 (0.02)	1.08 (0.02)	1.09 (0.03)	1.04 (0.02)
TPP (g l^{-1})	65.1 (7.8)	63.5 (8.6)	59.7 (8.2)†	57.4 (7.3)†
Albumin (g l^{-1})	46.9 (8.7)	45.1 (7.69)	41.8 (4.8)†	38.2 (5.7)†

Table 3 Coefficients (b_i), standard errors and corresponding values of F and P for the fitted $Y=b_0+b_1X_1+b_2X_2+b_3X_3+b_4X_4$, where Y=the peak twitch depression; X_1=age in yr; X_2=body weight in kg; X_3=log dose in μg kg^{-1}; and X_4=1 for females, 0 for males

Predictors	Coefficient	SE	F	P
Intercept	−1.8825	0.098	—	—
Age (yr)	0.0026	0.002	1.63	0.203
Weight (kg)	0.098	0.04	3.48	0.0587
Log dose (μg/kg)	4.54	0.144	991.2	<0.0001
Gender (F:M)	0.52	0.065	64.7	<0.0001

Table 4 Dose-response data. Values are mean (SD). *$P<0.01$ compared with male patients

	Males (n=30)	Female (n=30)
ED_{50} (μg kg^{-1})	23.9 (4.7)	18.4 (3.7)*
ED_{90} (μg kg^{-1})	45.4 (11.2)	33.5 (7.8)*
ED_{95} (μg kg^{-1})	55.7 (14.3)	39.8 (9.6)*
Slope (probit/log)	4.4 (0.7)	4.7 (0.8)

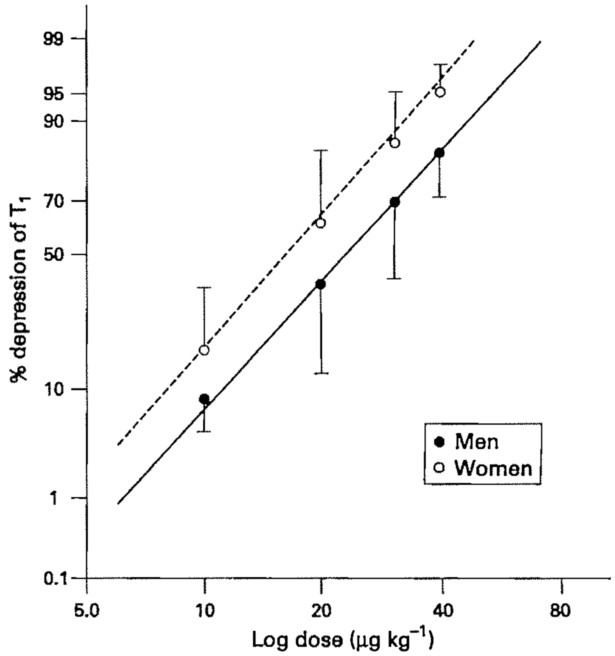

Figure 1 Dose-response curves of vecuronium in men and women. Points express the mean depression of T_1 after administration of each dose of vecuronium. Vertical bars represent SD.

T_1 following each dose of vecuronium. However, there were significant correlations between the peak depression of T_1 and gender, and the peak depression of T_1 and the cumulative log doses of vecuronium (table 3). The effect of interactions between gender and log doses was tested and no significance was achieved, thereby supporting the assumption that the regression lines for the two genders were parallel. The mean percentage depression of T_1 after administration of vecuronium 10, 20, 30, and 40 μg kg^{-1} was 8.1 (5.0), 39.3 (17.8), 68.3 (16.1), and 84.3 (8.8)% respectively in men, and 15.1 (11.4), 58.8 (16.4), 84.9 (10.6) and 93.8 (5.3)% in women. In each instance, the difference betwen the two groups was significant ($P<0.05$).

The cumulative dose-response curve of vecuronium in men was shifted in a parallel fashion to the right (fig. 1), indicating a reduced sensitivity to vecuronium-induced neuromuscular block compared with women. The effective doses calculated by linear regression are shown in table 4. There were significant differences in the ED_{50}, ED_{90} and ED_{95} of vecuronium between men and women. However, the slope of the dose-response curve of vecuronium in the males was not significantly different from that in females.

Using post-tetanic count stimulation at 50 Hz, all the patients were shown to have 100% depression of the twitch response after receiving a total dose of vecuronium 80 μg kg^{-1}. Vecuronium-induced neuromuscular block was significantly longer in women than in men. The duration of peak effect, clinical duration and total duration differed significantly between the two groups. However, the recovery index in the males did not differ from that in the females (table 5).

Discussion

The aim of this study was to determine if there was any difference between the sexes in the dose-response data and the time-course of action of vecuronium. We used strict exclusion criteria and controlled other factors known to interfere with

Table 5 Vecuronium pharmacodynamic data in patients with 100% neuromuscular block following administration of a total dose of 80 μg kg^{-1}. Duration of peak effect=time from completion of injection to recovery of T_1 to 5%; clinical duration=time from injection to 25% recovery; total duration=time from injection to 90% recovery; recovery index=time from 25% to75% recovery. Values are mean (SD). *$P<0.005$ compared with male patients

	Male (n=30)	Female (n=30)
Duration of peak effect (min)	18.7 (7.1)	26.0 (7.2)*
Clinical duration (min)	26.6 (8.8)	37.1 (11.2)*
Recovery index (min)	16.5 (7.0)	19.7 (8.1)
Total duration (min)	50.6 (16.0)	65.9 (20.7)*

neuromuscular block: there was no significant difference in the distribution of age or weight in the two groups and all the patients were Chinese of the Han race; the study drug was produced in Oss, Netherlands, in a single factory; the output variable, percentage twitch depression, was measured using the same neuromuscular function monitor in all patients; all the anaesthetic agents were given by the same anaesthetist and comparable anaesthetic equipment and drugs were used in all the subjects; and end-tidal carbon dioxide was kept in the normal range.

We used the incremental cumulative dose technique to evaluate the dose-response relation of vecuronium. Some investigators have found that the cumulative dose technique may underestimate the potency of neuromuscular blocking drugs that are rapidly distributed and eliminated.[18–20] However, the use of vecuronium was consistent throughout the study, and thus the degree of redistribution would have been similar in the two groups of patients. To improve the accuracy of the cumulative dose-response technique for vecuronium, we also restricted the number of doses to three.[15] The aim of the study was not to provide an absolute potency estimate, but to determine any sex-related effect on the neuromuscular block produced by vecuronium. When all patients in the present study are considered together, the mean effective doses and clinical duration of vecuronium are similar to the results of previous studies using a nitrous oxide–opioid technique without any potent inhalation anaesthetics.[9 19 21 22]

Our results showed that women were significantly more sensitive to vecuronium than men. The ED_{50}, ED_{90} and ED_{95} of vecuronium in the women were decreased by 23%, 26% and 29% respectively compared with the men, and the duration of peak effect, clinical duration, and total duration were prolonged by 39%, 40%, and 30%. These results are in keeping with those of previous studies in which there were also sex-related differences in the pharmacodynamic data on vecuronium.[13 14] In addition, pancuronium 100 μg kg^{-1}, the monoquaternary analogue of vecuronium, has a shorter onset time in women than men. However, Gramstad and Lilleaasen[15] demonstrated that there was no difference in pharmacodynamic responses to vecuronium and pancuronium between men and women. The differences among these studies are possibly attributable to differences in selection of samples, anaesthetic techniques and observation methods.

The exact reason for the differences in the sensitivity to vecuronium between the sexes is still unclear. The most likely reason in this respect is the known difference in body build between the sexes, men having a greater percentage of muscle mass and a lower percentage of fat than women.[23] A larger dose of neuromuscular blocking drug is needed when there is less fat and more muscle.[24] The volume of distribution, in ml kg^{-1}, is most likely decreased by the presence of more adipose tissue in females. A lower dose of muscle relaxant is required to produce the comparable neuromuscular block when the volume of distribution is decreased. In addition, vecuronium is mainly eliminated by the liver and there are sex-related differences in the activity of certain microsomes in the liver. Previous studies demonstrated that some drugs, which are mainly eliminated by the liver, are more rapidly metabolized and produce lower plasma levels in men than in women.[25]

The pharmacological effect of a drug is highly dependent on the degree of plasma protein binding. Duvaldestin and Henzel[26] showed that the protein-bound fraction of vecuronium was 30% and vecuronium is mainly bound to plasma albumin. Our results showed that the concentrations of total plasma protein and albumin were higher in the men than in the women ($P<0.01$). Following administration of vecuronium, the concentration of unbound drug and the ratio of the protein-unbound/bound in plasma were increased in the females because of their lower concentration of plasma protein. The increase in the unbound fraction of vecuronium in the women makes more drug available to the tissue and receptor sites.

In conclusion, this study suggests that there are gender-related differences in the dose-response and pharmacodynamics of vecuronium. Women were significantly more sensitive to vecuronium than men, requiring about 30% less drug to achieve the same degree of neuromuscular block. After the same dose of vecuronium, the clinical duration was significantly longer in the women compared to the men.

Acknowledgements

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British Journal of Anaesthesia 1998; 80: 725–732

Quantitative electroencephalographic analysis of the biphasic concentration–effect relationship of propofol in surgical patients during extradural analgesia

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Summary

We studied effects on the EEG of propofol infused at a rate of 0.5 mg kg^{-1} min^{-1} for 10 min in 10 healthy male surgical patients under extradural analgesia. The EEG amplitude in six frequency bands was related to arterial blood propofol concentrations and responsiveness to verbal commands. The EEG amplitude showed a characteristic biphasic response to increasing blood propofol concentrations in all frequency bands. During the infusion, patients lost responsiveness when EEG amplitudes in the high frequency bands were decreasing after having reached a maximum. EEG changes were different during infusion and emergence. Pharmacodynamic modelling, using two effect compartments with dissimilar equilibration constants, resulted in satisfactory fits. We conclude that propofol exerts a biphasic effect on the EEG amplitude in all frequency bands. The dissimilarity of EEG changes during infusion and during emergence suggests that two effect compartments with different equilibration constants exert opposing effects on the EEG. (*Br. J. Anaesth.* 1998; **80**: 725–732)

Keywords: monitoring electroencephalography; pharmacodynamics; propofol; biphasic modelling

Sedative doses of propofol significantly increase amplitude and power in the beta region of the EEG.[1 2] Hypnotic doses of propofol, however, cause slowing of the EEG, manifested by an increase in delta power, reduced alpha and beta activity, and a lowering of the median frequency and spectral edge.[3] This biphasic pattern of the EEG amplitude in the beta band in response to an increasing blood propofol concentration has been described qualitatively,[4 5] but has not been studied quantitatively.

The aims of the present study were, first, to quantify the biphasic relationship between propofol concentration and EEG effects during the transition from the awake state to hypnosis and during subsequent emergence and second, to fit a pharmacodynamic model to the observed changes. The study of EEG changes caused by hypnotics in anaesthetized surgical patients is hindered by the effects of concurrently administered sedative and analgesic drugs. As extradural analgesia with bupivacaine appears to have no significant effect on the EEG,[6] the study was performed in surgical patients under extradural analgesia, who received a 10-min propofol infusion.

Patients and methods

The study was approved by the Medical Ethics Committee of the University Hospital of Groningen. After obtaining written informed consent, we studied 10 healthy male patients, of mean (SD) age 28.4 (7.7) yr, weight 81 (12) kg and height 1.82 (0.12) m, scheduled for elective lower-limb surgery under extradural analgesia. Patients with a history of recent drug intake, an alcohol intake in excess of 30 g day^{-1}, neurological disturbances, or extreme nervousness were excluded. No oral intake was allowed after midnight preceding the operation. No premedication was administered.

Before operation, an i.v. cannula was inserted and 0.9% saline 500 ml infused as fluid loading. Extradural analgesia was achieved by giving 0.5% bupivacaine 20 ml through an extradural catheter inserted at L3–L4 5 min after a test dose of 0.5% bupivacaine 3 ml with epinephrine 15 mg. Forty min after the extradural administration of bupivacaine, i.v. administration of propofol 0.5 mg kg^{-1} min^{-1} was started with a constant-rate infusion for 10 min (total dose 5 mg kg^{-1}). Surgery was started after the patient lost responsiveness.

A 3-lead ECG, automatic noninvasive arterial pressure, oxygen saturation and end-tidal carbon dioxide concentration were monitored continuously. If ventilation became insufficient during the infusion of propofol, as indicated by Sp_{O_2} below 92% , an obstructed airway, or an end-tidal carbon dioxide concentration of more than 6%, ventilation was assisted manually with a face mask and oxygen-enriched air (40% O_2).

Responsiveness was determined by testing the response of the patient to simple commands from a prerecorded tape ("raise your thumb", "spread your fingers", and "clench your fist"), given via headphones every 30 s. It was noted when the patient became unresponsive, and when responsiveness returned after stopping the propofol infusion.

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Table 1 Pharmacokinetic values expressed as mean (SD)

	Three compartments (n=7)	Two compartments (n=3)
$t_{1/2}\pi$ (min^{-1})	1.00 (0.52)	1.33 (0.31)
$t_{1/2}\alpha$ (min^{-1})	9.54 (4.34)	
$t_{1/2}\beta$ (min^{-1})	74.4 (19.1)	55.2 (12.4)
V_c (l kg^{-1})	0.10 (0.04)	0.09 (0.09)
V_{ss} (l kg^{-1})	1.31 (0.30)	1.45 (0.83)
Cl (ml kg^{-1} min^{-1})	28.2 (5.39)	32.5 (6.11)

EEG RECORDING AND ANALYSIS

The EEG was recorded from bilateral mastoid to prefrontal leads, M_1–Fp_1 and M_2–Fp_2, with Fp_z as reference, using standard ECG electrodes (Red Dot) on the skin, prepared with Omni-prep abrasive paste. Electrode impedance was maintained below 5 kΩ. A 5-min baseline EEG was recorded before starting extradural analgesia, with the patient supine and with the eyes closed. After the onset of analgesia, the EEG was recorded continuously from 5 min before the start of the propofol infusion until the patient regained consciousness and thereafter intermittently for 5-min periods, coinciding with blood sampling, until 190 min after the start of the infusion. The raw EEG signal was stored on FM tape for off-line analysis. The EEG was processed with aperiodic analysis[7] (Lifescan software version 4.3, Diatek, San Diego, CA) to derive the amplitude and frequency characteristics of sequential EEG waves. Data recorded from the nondominant hemisphere (defined on the basis of the handedness of the patient) were used for analysis. Amplitudes in six frequency bands (0–5, 6–10, 11–15, 16–20, 21–25, and 26–30 Hz) were averaged over periods of 15 s. Periods containing EMG artefact, manifest as an amplitude of more than 15 mV s^{-1} in the frequency band 26–30 Hz, were excluded from analysis. The time course of the amplitudes in the six frequency bands was studied and related to the blood propofol concentrations, the time at which the patient became unresponsive to verbal command, and the time at which responsiveness was regained.

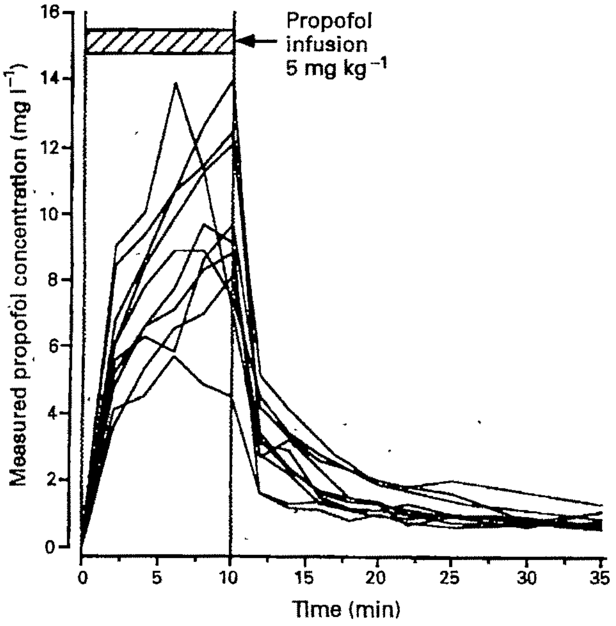

Figure 1. Measured blood propofol concentrations during the first 35 min after the start of the propofol infusion. Infusion rate 0.5 mg kg^{-1} min^{-1}. Duration 10 min (total dose 5 mg kg^{-1}). Linear interpolation between measured data points was applied to draw lines.

PROPOFOL KINETICS AND DYNAMICS

A 20 gauge cannula was inserted in a femoral artery for sampling of arterial blood after the onset of extradural analgesia. This sample site was chosen to minimize patient discomfort. Blood samples of 3 ml were taken at 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 30, 40, 55, 70, 100, 130, and 190 min after the start of the propofol infusion and mixed with EDTA. Blood samples were stored at 4°C until determination of whole-blood propofol concentrations with high performance liquid chromatography (detection limit 5 μg l^{-1}, coefficient of variation 4.3 %).[8]

Bi- and tri-exponential functions were fitted to concentration *vs* time data using weighted (log concentration) least-squares nonlinear regression analysis (software package Multifit, J. H. Proost, University of Groningen, The Netherlands). A bi- or tri-exponential function was chosen on the basis of the Schwartz criterion.[9] The following pharmacokinetic parameters were derived using standard equations: volume of the central compartment (Vc), volume of distribution at steady state (Vss), plasma clearance (Cl), distribution ($T_{1/2}\pi$, $T_{1/2}\alpha$) and elimination ($T_{1/2}\beta$) half-lives. Fitted data of individual patients were used to calculate the time course of the blood propofol concentration in each patient, to estimate the propofol concentrations at the time of loss and return of responsiveness, and at the time of the EEG amplitude maxima.

For pharmacokinetic–dynamic modelling of the biphasic EEG effects of propofol the parametric modelling technique of Mandema[10] was applied. This model assumes that the measured EEG effect of propofol is the result of effects of propofol on two different effect compartments. Increasing propofol concentrations in these two effect compartments have opposing effects on the EEG amplitude, for example, activation and inhibition. The formula of the relationship between effect (E), and concentration is:

$$E = \left(E_0 + \frac{E_{max} C_1^{\gamma}}{EC_{50}^{\gamma} + C_1^{\gamma}}\right)\left(1 - \frac{C_2^{\gamma}}{EC_{50}^{\gamma} + C_2^{\gamma}}\right)$$

where E_0 is the baseline effect, E_{max} is the hypothetical maximal increase of EEG effect when no EEG inhibition would occur, EC_{50} is the steady state concentration at which half of E_{max} occurs, C_1 is the concentration in effect compartment 1, C_2 is the concentration in effect compartment 2, and γ determines the slope of the curves. The concentration in the effect compartments was calculated using the following equation:

$$\frac{dC_e}{dt} = k_{eo} (C_p - C_e)$$

where C_e is the concentration in the hypothetical effect compartment, C_p is the blood concentration, and k_{eo} is a first-order rate constant, describing the rate of equilibration between the plasma and the effect site. C_p values were calculated using linear

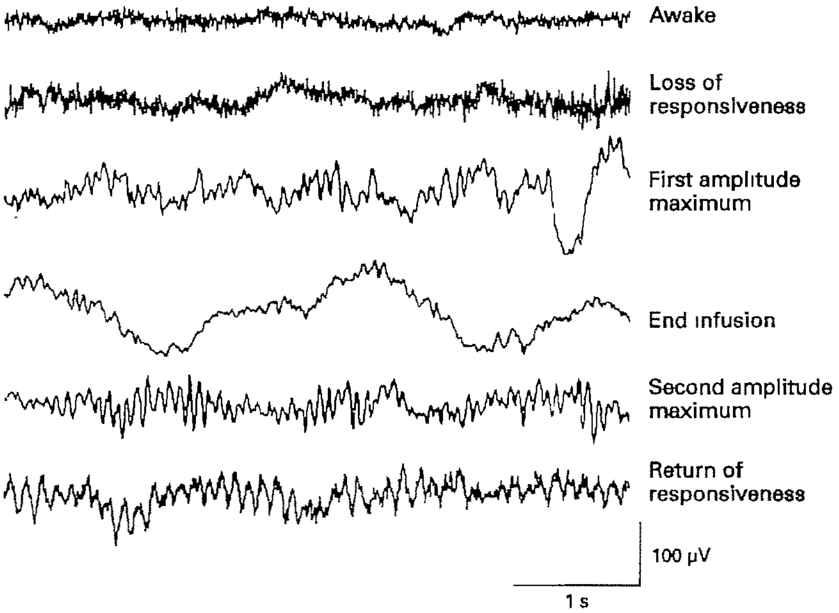

Figure 2 Typical analogue EEG recordings of a patient (no. 6) at representative moments during the propofol infusion and emergence. First amplitude maximum, second amplitude maximum=times when maxima in the 11–15 Hz frequency band were reached: first, during infusion; second, during emergence.

interpolation between measured C_p values during infusion and log-linear interpolation between the measured C_p values after the infusion. In the present study we allowed one or two values for k_{e0} during fitting. When only one k_{e0} is allowed the concentrations in C2 and C1 are identical and the model could be considered to consist of one effect compartment. The quality of fit was expressed as the coefficient of determination, R.

$$R^2 = 1 - \frac{\sum(E_{observed} - E_{modelled})^2}{\sum(E_{modelled} - E_{average})^2}$$

STATISTICAL ANALYSIS

As it could not be ascertained if the EEG amplitude data derived from aperiodic analysis in 10 patients were normally distributed, EEG data are presented as medians and 25–75 percentiles. Pharmacokinetic data are expressed as mean (SD). Pharmacodynamic data are expressed as mean (SD) and median and 25–75 percentiles. EEG data and the coefficients of correlation, R^2, of the pharmacodynamic fits using one or two values for k_{e0} were compared using the Wilcoxon signed ranks test. Blood propofol concentrations at which EEG amplitudes in the four frequency bands from 0 to 20 Hz reach their maximum were compared using the Friedman test. $P<0.05$ was considered significant. The computer program SPSS for Windows version 6.13 was used for statistical calculations.

Results

Extradural analgesia was adequate in all patients (sensory level to cold: T9 (T12–T5), median and range). No patient developed bradycardia (<50 beats min^{-1}) or hypotension (lowering of systolic blood pressure by >25% from the average of the systolic blood pressures measured at hospital admission, on the morning of the operation, and on arrival at the anaesthetic room). Shivering was observed in four patients after the onset of extradural analgesia. All patients required assisted ventilation from approximately 1 min after loss of responsiveness for 22 (16–29) min (median and 25th–75th percentile). Patients became unresponsive 2.8 (2.5–3.4) min after the start of the propofol infusion and regained consciousness 21.5 (16.1–25.4) min after the infusion was stopped. The blood propofol concentrations, calculated on the basis of individual pharmacokinetic

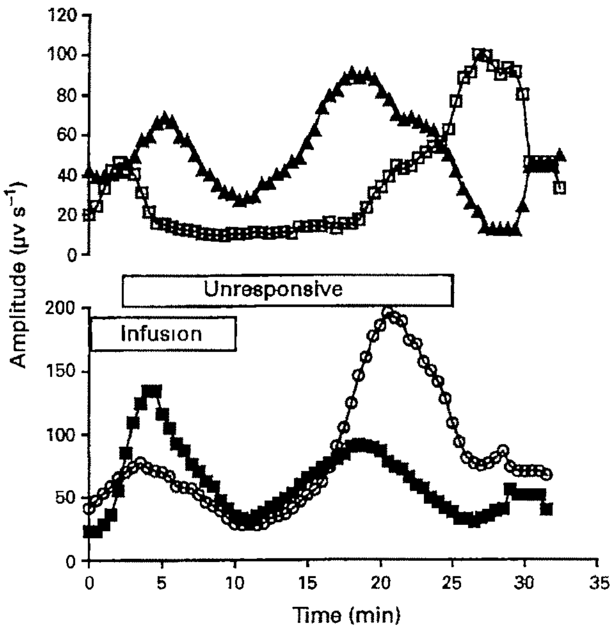

Figure 3 Representative time course of EEG amplitude in four frequency bands in a patient (no. 9) in response to a 10-min infusion of propofol 0.5 mg kg^{-1} min^{-1}. All four frequency bands show two amplitude maxima, one during the infusion and a second during emergence. In each frequency band, there is a difference in amplitude between the first amplitude maximum and the second. This patient was unresponsive from 2.5 min until 24.5 min after the start of the infusion. Frequency bands: ▲=6–10 Hz; □=16–20 Hz; ■=0–5 Hz; ○=11–15 Hz.

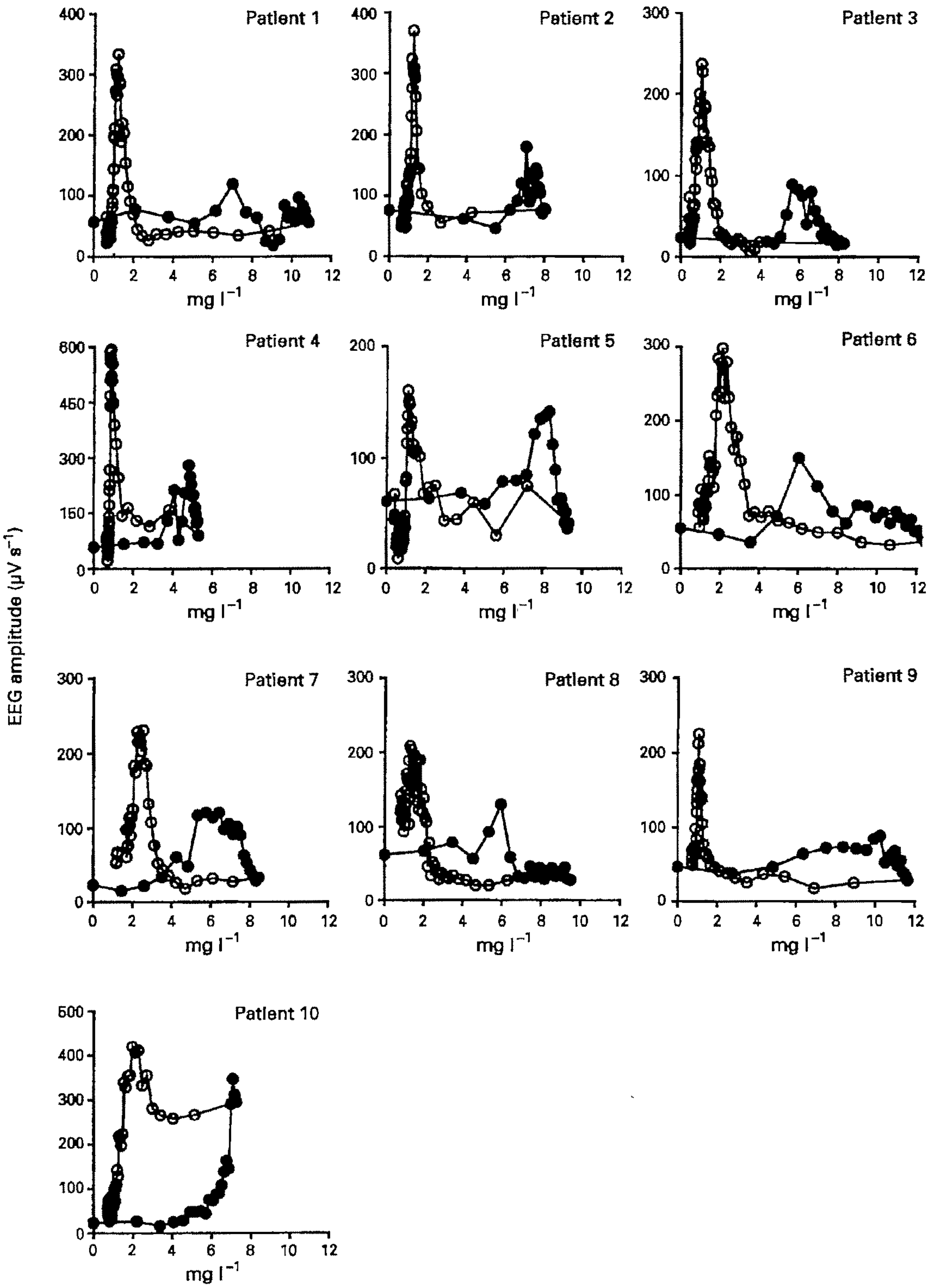

Figure 4 Hysteresis curves of EEG amplitude in the 11–15 Hz frequency band *vs* calculated blood propofol concentrations during infusion and during emergence. The amplitude maximum is smaller when blood propofol concentrations are increasing than when they are decreasing. Patient no. 10 showed only a minimal biphasic effect, possibly because lower blood propofol concentrations were reached during the infusion. ●=during infusion; ○=after infusion.

modelling, at the times when consciousness was lost and regained were 6.45 (5.87–7.01) and 0.85 (0.64–1.09) mg l^{-1} respectively. The measured blood propofol concentrations in individual patients during the infusion and the first 25 min after the infusion are shown in figure 1. The calculated pharmacokinetic parameters are shown in table 1.

The awake EEG was characterized by predominant activity in the 8–14 Hz frequency range. The EEG pattern did not change after the onset of extradural analgesia, although amplitude in the high-frequency bands increased in the patients who were shivering. After the start of the infusion, the amplitude in the high-frequency bands increased initially. With further increases in blood propofol concentration the EEG slowed and amplitude decreased. At the end of the infusion, slow-wave activity was present with spindles of high-frequency

Table 2 EEG amplitudes before, during and after a 10-min propofol infusion of 30 mg kg^{-1} h^{-1} and times of loss of responsiveness, maximum EEG amplitude, and return of responsiveness. *Different from baseline value; †different from maximum during infusion, ††different from the time of loss of responsiveness. Data are expressed as median and 25^{th}–75^{th} percentile

Frequency band	0–5 Hz	6–10 Hz	11–15 Hz	16–20 Hz
EEG amplitude (µV s^{-1})				
Baseline	44 (24–69)	51 (19–76)	42 (17–53)	9 (2–27)
After epidural analgesia	40 (35–62)	40 (31–54)	42 (32–71)	31* (7–38)
Loss of responsiveness	87* (46–99)	43 (32–70)	86* (69–137)	52* (19–84)
Maximum during infusion	126* (71–190)	71* (46–137)	106* (76–269)	54* (20–99)
End of infusion	52* (29–119)	34 (24–123)	43 (23–210)	11 (4–20)
Maximum during emergence	99*† (65–125)	93* (74–136)	242*† (163–477)	46* (17–96)
Return of responsiveness	45 (28–57)	31 (20–50)	70* (32–142)	17 (5–85)
Time (min)				
Loss of responsiveness	2.8 (2.5–4.5)			
Amplitude maximum during infusion	4.8†† (3.5–9.0)	6.0†† (4.0–8.5)	3.8 (1.5–8.0)	2.5†† (0.5–4.0)
Amplitude maximum during emergence	16.8 (10.5–20.8)	17.0 (11.5–20.8)	19.3 (15.3–24.8)	21.8 (14.8–30.5)
Return of responsiveness	31.5 (23.8–39.5)			

activity. During emergence, high-amplitude high-frequency activity reappeared, followed by a decrease in amplitude until the patient became responsive (fig. 2).

Quantitatively, marked amplitude changes occurred in the frequency bands between 0 and 20 Hz, but amplitude in the frequency bands between 21 and 30 Hz was small and often contained obvious muscle artefacts when patients were responsive. Therefore data calculated from these bands were not used in the calculations and are not shown in the tables and figures. In all four frequency bands below 21 Hz, EEG amplitude showed a biphasic response to increasing blood propofol concentration, that is, EEG amplitude initially increased and subsequently decreased to or beyond baseline values. When the infusion was stopped, EEG amplitude again showed a biphasic response: it increased to a maximum and then decreased until the patient became responsive (fig. 3).

The amplitude at the moment the patient became responsive was similar to or just above baseline values. The amplitude maxima reached during the infusion and during emergence were dissimilar in the 0–5 Hz and 11–15 Hz bands (table 2).

Hysteresis of the EEG effect–blood concentration curve was observed. Figure 4 shows individual hysteresis curves of EEG amplitude in the 11–15 Hz band and calculated blood concentrations during and after the infusion.

The blood concentrations at which the EEG amplitude reached its maximum during infusion and emergence varied in different frequency band. EEG amplitudes in higher bands reached their maximum at lower blood propofol concentrations than the EEG amplitudes in lower-frequency bands ($P<0.01$) (fig. 5).

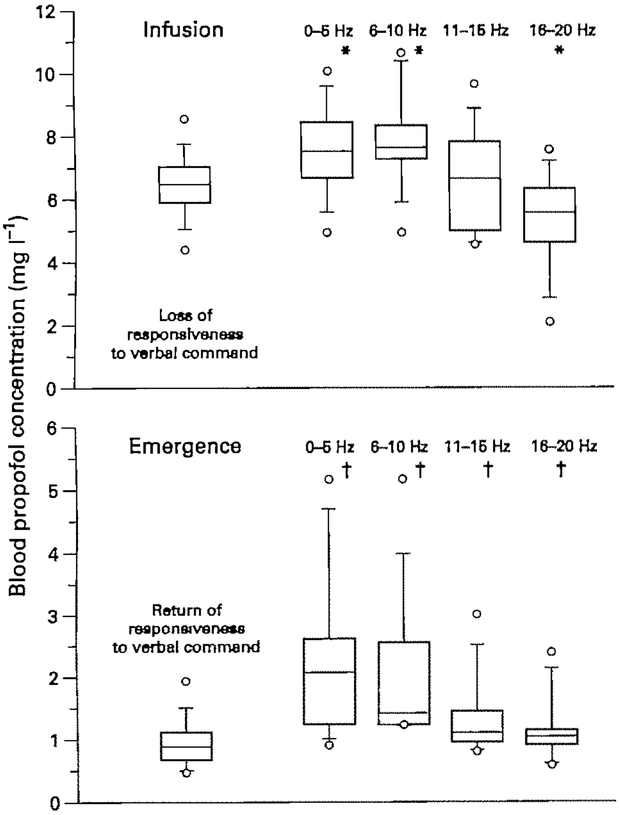

Figure 5 Box plots of calculated blood propofol concentrations at the times of loss and regaining of responsiveness, and when EEG amplitude maxima were reached in the frequency bands 0–5, 6–10, 11–15, and 16–20 Hz during infusion and emergence. With increasing frequency the maxima occurred at lower blood concentrations. Box plots represent median, 25th–75th percentile, 10th–90th percentile, and lowest and highest values (open circles). *$P<0.01$ compared with loss of responsiveness to verbal command. †$P<0.01$ compared with return of responsiveness to verbal command.

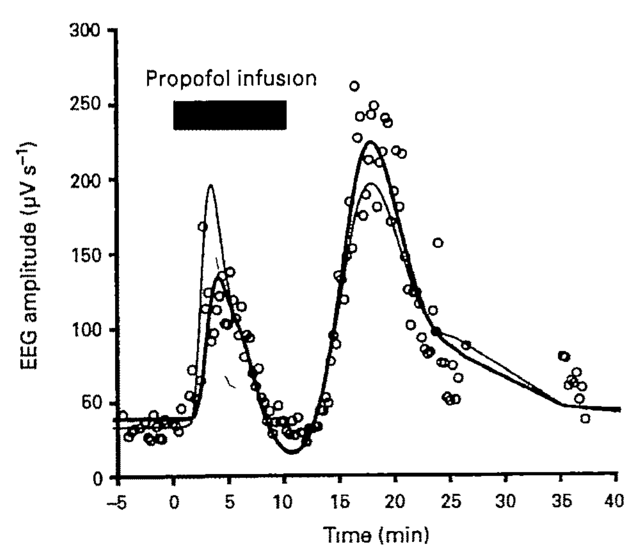

Figure 6 Observed and estimated EEG amplitude in the frequency range 11–15 Hz vs time in patient no 7. Estimated values were obtained by fitting measured amplitudes to the Mandema biphasic pharmacodynamic model, allowing either one or two values for k_{e0}. o=observed effect. Allowing one k_{e0} resulted in identical maximal EEG amplitudes during and after infusion and an R^2 of 0.78 (thin line). Allowing two values for k_{e0} resulted in a smaller maximal EEG amplitude during infusion and an R^2 of 0.87 (thick line).

Table 3 Pharmacodynamic parameters of individual patients estimated with the Mandema model for the frequency band 11–15 Hz allowing two values for k_{eo}. * $P<0.01$ *vs* $k_{eo}1$

Patient	R^2	$k_{eo}1$ (min^{-1})	$k_{eo}2$ (min^{-1})	EC_{50} (mg l^{-1})	γ	E_0 (μV s^{-1})	E_{max} (μV s^{-1})
1	0.91	0.06	0.08	4.0	10.8	39	1775
2	0.87	0.16	0.25	4.1	4.2	62	932
3	0.89	0.21	0.27	2.0	3.8	21	563
4	0.91	0.15	0.21	2.4	5.3	26	1995
5	0.82	0.22	0.21	3.6	3.7	25	525
6	0.87	0.05	0.07	4.7	16.4	79	4356
7	0.87	0.27	0.34	3.6	4.8	39	667
8	0.83	0.07	0.16	3.1	4.1	52	446
9	0.89	0.13	0.18	3.4	3.5	37	491
10	0.92	0.17	0.22	4.9	5.6	46	1686
Mean	0.88	0.15	0.20	3.6	6.2	43	1344
SD	0.03	0.07	0.08	0.9	4.2	18	1213
Median	0.88	0.16	0.21*	3.6	4.5	39	800
25th Percentile	0.87	0.07	0.16	3.1	3.8	26	525
75th Percentile	0.91	0.21	0 25	4.1	5.6	52	1775

Loss of responsiveness occurred immediately after the initial amplitude maximum in the 16–20 Hz band and before or simultaneously with the initial amplitude maximum in the 11–15 Hz band. Patients regained consciousness after the second amplitude maximum in the 11–15 Hz band and the 16–20 Hz band. As the EEG amplitude had a biphasic response to blood propofol concentrations, responsiveness to verbal command could not be related to an amplitude value in any frequency band without information on the time course of the value.

Calculated pharmacodynamic parameters derived from EEG amplitudes in the 11–15 Hz band of individual patients allowing two values of k_{eo} are shown in table 3.

The two-effect compartment model fitted the data significantly better than the one-effect compartment model in both the 11–15 Hz band and the 0–5 Hz band (median $R = 0.88$ *vs* 0.79 in the 11–15 Hz band, and 0.78 *vs* 0.68 in the 0–5 Hz band, $P<0.01$). Figure 6 shows an example of the one- and two-compartment model fitted to the EEG data in the 11–15 Hz frequency band.

EC_{50} was higher in the 0–5 Hz band: 4.2 (3.2–4.5) mg l^{-1} *vs* 3.6 (3.1–4.1) mg l^{-1} in the 11–15 Hz band. In the 0–5 Hz band $k_{eo}1$ was larger than $k_{eo}2$: 0.27 (0.22–0.33) min^{-1}. In the 11–15 Hz band, however, k_{eo} was smaller than $k_{eo}2$: 0.16 (0.07–0.21) min^{-1} *vs* 0.21 (0.16–0.25) min^{-1}.

Discussion

In this study, during a 10-min infusion of propofol, we observed a biphasic EEG amplitude response to an increasing blood propofol concentration in all frequency bands. EEG amplitude maxima were dissimilar during infusion and emergence in two of the four frequency bands. The blood propofol concentration at which the EEG amplitude maximum in a particular frequency band occurred was inversely related to the frequency of this band.

A biphasic EEG response to increasing blood propofol concentrations was first described by Hazeaux and colleagues,[4] who reported an increase followed by a decrease in alpha amplitude, and the appearance of theta and delta activity after an injection of propofol 2.5 mg kg^{-1} in 30 s. Borgeat and co-workers[5] described similar changes during induction of anaesthesia in children with a propofol bolus of 3 or 5 mg kg^{-1}. They found a transient shift from predominantly alpha (9–10 Hz) activity to beta (>14 Hz) activity, followed by continuous delta activity. Hazeaux and Borgeat did not quantify the EEG changes or determine blood propofol concentrations at which these phenomena occurred. In the presence of sedative propofol blood concentrations, an increase in beta activity accompanied by an increased sedation level has been reported.[1 2] In both studies, propofol was given in doses sufficient to achieve sedation, and the infusion rate was adjusted to prevent unconsciousness. Beta activity was increased throughout the procedure and showed no biphasic response, probably because the patients did not become unconscious and blood propofol concentrations were 0.69 (0.34) mg l^{-1}[1] and 1.14 (0.39) mg l^{-1}.[2] In the presence of anaesthetic propofol concentrations, Schwilden and colleagues[3] used the median frequency, calculated from the power spectrum, as the EEG effect parameter for closed-loop feedback control of propofol anaesthesia. They described a monophasic response to propofol, that is, a decrease of median frequency with increasing blood concentrations. More recently, Forrest and co-workers[11] reported a biphasic shift of median frequency shortly after the start of a propofol infusion. These authors were unable to quantify the maximum in median frequency because they collected insufficient data in this concentration range.

The biphasic EEG amplitude response in the 11–15 Hz and the 16–20 Hz bands observed in the present study is consistent with the increased beta activity found by others during sedation,[1 2] and the decreased median frequency described during anaesthetic propofol concentrations.[3 11]

Although we were unable to demonstrate an influence of extradural analgesia on the EEG in a previous study,[6] in the present study we observed an increase in amplitude of the 16–20 Hz band. As shivering occurred in four patients, we suspect that this increase in amplitude in the 16–20 Hz band is the result of EMG artefact. EEG amplitude in the other frequency bands was not different from baseline values. The 30 Hz low-pass filter probably eliminates EMG artefacts caused by shivering in the other frequency bands. Although extradural analgesia has no effect on EEG amplitude itself, synergistic effects of extradural analgesia with propofol on the EEG amplitude cannot be excluded.

Extradural analgesia might have influenced the pharmacokinetics of propofol. Haemodynamic changes, venous pooling and hepatic blood flow can affect its distribution and clearance. In comparison with the pharmacokinetic data reported by other investigators[12 13 14], we observed a shorter $T_{1/2}\pi$ and $T_{1/2}\beta$ and a smaller Vss. In addition to the effects of extradural analgesia, a short sampling period may have been responsible for these differences. However, changes in pharmacokinetic parameters had no influence on the estimation of pharmacodynamic parameters, as measured blood propofol concentrations were used to calculate effect compartment concentrations.

The sigmoid E_{max} model has been applied successfully for pharmacodynamic modelling of plasma concentration–effect relationships of opioids[15] and hypnotics.[5 16] However, modelling of biphasic effects remains a major challenge. One might transform EEG data in such a way that a sigmoid E_{max} model fits the data. Greg and colleagues suggested semilinear canonical correlation,[17 18] which uses a summation of log-transformed EEG power in several frequency bins, which are multiplied by a weight factor to yield effect data. When we applied this method to our data, we achieved weight factors for individual patients that resulted in good fits in nine of the 10 patients (R^2=0.97 (0.95–0.97). However, when the weight factors of all patients were averaged and the average weight factor was applied to the EEG data, the sigmoid E_{max} model could not be fitted satisfactorily (R^2=0.78 (0.59–0.89). Ebling and colleagues[19] have described the application of a nonparametric approach to characterize biphasic EEG effects in response to thiopentone in rats. The method describes the relationship between the concentration of drug in the effect compartment (C_e) and distinct EEG effects including baseline effect, maximal effect, 50% of baseline effect, and burst suppression. However, nonparametric estimation of k_{eo}, needed to calculate the effect site concentrations, is based on the assumption that the effect during increasing and decreasing effect compartment concentrations is similar.[20 21] As the magnitude of EEG effects during and after the infusion in the present study was dissimilar in the 0–5 Hz band and the 11–15 Hz band, nonparametric estimation of k_{eo} and effect site concentrations was not possible. Accordingly, we did not attempt to use this method to model the effect of propofol.

It could be that we observed dissimilar EEG amplitude maxima during infusion and during emergence in the present study because the 15 s averaging epoch used was too long to detect a transient increase in amplitude in response to a rapidly changing propofol concentration. This could explain the lower EEG maximum during infusion in the 11–15 Hz band, when concentrations changed rapidly. However, the amplitude maximum in the 0–5 Hz band was highest during infusion, in spite of the same rapid concentration changes. Another argument against this explanation is that the amplitude maxima in the 11–15 Hz band did not change and remained smallest during infusion after reanalysis of the data using 2 s epochs.

The dissimilar EEG amplitude maxima during infusion and emergence suggest that more than one effect compartment may exist. One might hypothesise two compartments with different equilibration constants exerting opposing effects: inhibition and activation. Applying this concept to the EEG amplitude in, for example, the 11–15 Hz range results in the following sequence: during an increasing blood propofol concentration, the concentration will rise faster in the "inhibiting" effect compartment than in the "activating" compartment, and therefore inhibition will dominate soon after the start of drug administration. However, after stopping the propofol infusion, the concentration in the "inhibiting" effect compartment will decrease more rapidly, thus allowing the "activating" effect to become clinically apparent.

Because dissimilar effects during increasing and decreasing blood concentrations preclude modelling with nonparametric models, we chose the simplest parametric model proposed by Mandema (with the least number of parameters to be estimated) to fit our data.[10]

Although the Mandema model is a simplification of the summation of two sigmoid E_{max} curves, it was possible to model the data consistently according to this method with good results.

The findings that using two values for k_{eo} resulted in significantly better fits than using one, and that there were significant differences between $k_{eo}1$ and $k_{eo}2$ supports the hypothesis that assuming two effect compartments with unequal equilibration constants might explain the dissimilar EEG amplitudes observed during infusion and emergence in the 0–5 Hz and the 11–15 Hz band.

One might hypothesize that differences in regional cerebral blood flow could be a physiological explanation for these differences. An alternative explanation might be that there are differences in the affinity or dissociation rate of propofol for receptors on either excitatory or inhibitory neurons. A third explanation might be that in either the excitatory or the inhibitory neuron, after initial occupation of the receptor, a secondary pathway must become activated, which requires additional time before an effect becomes apparent.

Because of the biphasic character of the EEG response to propofol, a particular EEG amplitude may correspond to more than one propofol concentration. This finding makes it difficult to use the EEG amplitude as an indicator of the level of consciousness. Estimation of the level of consciousness requires additional information about the time course of the EEG amplitude and the time course of the EEG amplitude in other frequency bands. For use as a control parameter of the level of consciousness one might try to maintain the EEG amplitude in the 0–5 Hz band at its maximal value, as these maxima correspond to propofol concentrations at which patients are unresponsive. When EEG amplitude decreases from the maximal value one can determine the direction of change of propofol concentration from the changes of EEG amplitudes in other frequency bands.

In conclusion, the propofol concentration–EEG effect relationship is biphasic in all EEG frequency bands. The present study demonstrates that the EEG effects during infusion and emergence are dissimilar, which suggests the existence of at least two effect compartments with different equilibration constants exerting opposing effects on EEG amplitude. Modelling of the blood propofol concentration–EEG relationship was possible using a biphasic parametric model.

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Effects of premedication on dose requirements for propofol: comparison of clonidine and hydroxyzine

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Summary

The influence of a single dose of clonidine (5 µg kg^{-1}) or hydroxyzine (1 mg kg^{-1}) on intraoperative propofol requirements was determined in 28 male patients (ASA I) undergoing elective orthopaedic surgery. Patients were randomly allocated to receive either clonidine or hydroxyzine orally 2 h before induction of anaesthesia. After a loading dose of propofol (2.5 mg kg^{-1}), mivacurium (0.2 mg kg^{-1}) and alfentanil (15 µg kg^{-1}), anaesthesia was maintained with a standardized propofol infusion supplemented with nitrous oxide (66%) in oxygen. During surgery, additional propofol boluses (1 mg kg^{-1}) were administered when heart rate or mean arterial pressure increased by more than 10% compared with preinduction values. The clonidine group demonstrated a 14.5% decrease in total propofol requirements ($P<0.05$) and a 52.2% reduction in additional propofol boluses ($P<0.02$) in comparison with the hydroxyzine group. Intraoperative heart rate and mean arterial presure were significantly lower in the clonidine group but no patients needed treatment with ephedrine for hypotension or bradycardia. Recovery of psychomotor function and discharge from the recovery room were not delayed in the clonidine group. This study indicates that 5 µg kg^{-1} clonidine given as premedication in ASA I patients reduces intraoperative propofol requirements in comparison with 1 mg kg^{-1} hydroxyzine without inducing adverse effects on recovery or haemodynamic stability. (*Br. J. Anaesth.* 1998; **80**: 733–736)

Keywords: anaesthesia i.v; anaesthetics i.v. propofol; premedication clonidine; premedication hydroxyzine

The primary goals of premedication are to relieve anxiety and produce sedation.[1] However, its effects are not restricted to the preoperative period. Preanaesthetic medication significantly modulates intraoperative requirements for anaesthetic agents such as the i.v. anaesthetic propofol.[2 3]

Alpha$_2$-adrenoreceptor agonists such as clonidine produce both preoperative sedation and anxiolysis,[4 5] and they have been proposed for premedication.[6] The potential advantages of using alpha$_2$-agonists preoperatively are: improved intraoperative haemodynamic stability[7 8]; attenuated sympathoadrenal responses to laryngoscopy;[9] reduced intraoperative requirement for opioids and volatile anaesthetics[7 8 10]; and less postoperative pain and shivering.[11 12] However, depending on the dose selected, they can induce marked bradycardia and hypotension and deep sedation, and can delay postoperative recovery.[13 14]

In a previous study, Richards and colleagues observed a reduction of intraoperative dose requirements for propofol in a small subgroup of patients receiving a large oral dose of clonidine (8.5 µg kg^{-1}) before propofol–alfentanil anaesthesia.[14] However, this was associated with a near doubling of postoperative recovery times. Therefore, we hypothesized that a lower clonidine dose may reduce intraoperative anaesthetic requirements without major adverse effects on arterial pressure and time of emergence from anaesthesia. The present study was designed to compare the effects of premedication with oral clonidine (5 µg kg^{-1}) or hydroxyzine (1 mg kg^{-1}) on, first, intraoperative dose requirements for propofol and, second, intraoperative haemodynamics and time of emergence from anaesthesia.

Patients and methods

After obtaining local ethical committee approval and written informed consent, we studied 28 ASA I male patients undergoing orthopaedic surgical procedures.

In this double-blind study, all premedication was given orally. The night before surgery, each patient received 1 mg kg^{-1} hydroxyzine. Two hours before induction of anaesthesia, patients were randomly allocated to receive either 5 µg kg^{-1} clonidine (Catapressan, Boehringer Ingelheim, Paris, France) (group C, $n = 16$) or 1 mg kg^{-1} hydroxyzine (Atarax, UCB pharma, Nanterre, France) (group H, $n = 12$). Exclusion criteria were age below 18 or above 50 yr, a potentially haemorrhagic surgical procedure, anticipated duration of anaesthesia less than 60 min or an underlying cardiovascular or psychiatric disease or medication.

Sedation, anxiety, heart rate and arterial blood pressure were recorded upon arrival in the operating room. Sedation was assessed by one investigator using a score derived from the Ramsay scale and

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Table 1 Patient characteristics, duration of anaesthesia, end-tidal nitrous oxide and total doses of alfentanil and mivacurium. Values are mean (SD) or groups mean (range)

	Hydroxyzine group	Clonidine group
Age (yr)	28 (19–41)	23 (18–33)
Weight (kg)	74 (14)	72 (10)
Height (cm)	175 (6)	178 (6)
Duration of anaesthesia (min)	93 (31)	99 (36)
Alfentanil (μg kg^{-1})	37 (8)	37 (10)
Mivacurium (mg kg^{-1})	0.21 (0.04)	0.2 (0.01)
End-tidal nitrous oxide (%)	57 (8)	62 (6)

Table 2 Intraoperative requirements for propofol (mean (SD)) or mean (range). $^*P<0.05$ and $^{**}P<0.02$ compared with the hydroxyzine group

	Hydroxyzine group	Clonidine group
Total propofol requirements (mg kg^{-1} h^{-1} anaesthesia)	10.3 (1.9)	8.8 (1.7)*
Propofol boluses for induction	1.1 (1–2)	1.0 (1–1)
Propofol boluses for maintenance (h^{-1} anaesthesia)	1.1 (0.7)	0.5 (0.6)**
Time spent at 4 mg kg^{-1} h^{-1} (min)	9.6 (12.7)	26.2 (20.7)**
Final propofol infusion rate (mg kg^{-1} h^{-1})	6.8 (2.3)	4.9 (1.6)**

ranging from grade 1 (awake and alert) to grade 6 (totally drowsy and uncommunicative).[15] Anxiety was estimated by the patient using a visual analogue scale (VAS) ranging from 0 to 100 mm. Use of the VAS was explained to each participant during the preoperative evaluation. Intraoperative monitoring consisted of ECG, automatic non-invasive arterial BP, pulse oximetry (Sp_{O_2}) and end-tidal carbon dioxide and nitrous oxide concentrations. Heart rate and arterial blood pressure measurements were recorded every 2 min until intubation and then every 5 min until the end of surgery. Anaesthesia was induced with propofol (2.5 mg kg^{-1}), alfentanil (15 μg kg^{-1}) and mivacurium (0.2 mg kg^{-1}). A second 1 mg kg^{-1} propofol dose was given if motor reaction occurred during laryngoscopy. After tracheal intubation, the lungs were mechanically ventilated with a mixture of 66% nitrous oxide and 34% oxygen to maintain end-tidal carbon dioxide between 3.73 and 4.67 kPa. Anaesthesia was maintained with a four-stage decremental infusion modified from that described by Roberts and colleagues.[16] It was started immediately after induction of anaesthesia and consisted of 10 mg kg^{-1} h^{-1} for 10 min, 8 mg kg^{-1} h^{-1} for 10 min, 6 mg kg^{-1} h^{-1} for 10 min and 4 mg kg^{-1} h^{-1} until skin closure. Bolus and maintenance doses of propofol were achieved using a volumetric infusion pump (Graseby 3400). A second 15 μg kg^{-1} alfentanil bolus was administered immediately before skin incision.

During surgery, depth of anaesthesia was considered insufficient if heart rate or mean arterial pressure increased by more than 10% compared with preinduction values. In this case, a 1 mg kg^{-1} propofol bolus was given and the maintenance infusion rate was increased by 2 mg kg^{-1} h^{-1} until sufficient depth of anaesthesia was restored. The propofol maintenance infusion rate was then set to its former value.

Ringer lactate solution, 10 ml kg^{-1}, was infused during the first hour of anaesthesia, followed by 5 ml kg^{-1} h^{-1} until the end of surgery. Intraoperative hypotension was defined as a arterial blood pressure below 65 mm Hg. Symptomatic bradycardia was considered as a heart rate below 45 beats min^{-1} with simultaneous hypotension. Both events were treated with ephedrine.

On completion of the surgical procedure, the time from the end of propofol infusion to extubation, response to verbal command and correct recall of date of birth were recorded. Time spent in the recovery room was also recorded. Patients were allowed to leave the recovery room if they met the following criteria: a sedation score of 1, a mean arterial pressure and heart rate that did not differ by more than 20% from preinduction values, an oxygen saturation greater than 95% while breathing room air for at least 10 min, a pain VAS score below 30 mm and the absence of shivering or agitation.

STATISTICAL ANALYSIS

Data are mean (SD) or mean (range). Quantitative variables were compared using the Mann–Whitney U test and categorical variables using the chi-square test. $P < 0.05$ was considered significant.

Results

Patient characteristics, duration of anaesthesia and doses of anaesthetic agents other than propofol are shown in table 1.

On arrival in the operating theatre, anxiety and sedation scores were similar for groups C and H: 29 (0–80) mm *vs* 36 (0–54) respectively for anxiety and 1.5 (1-2) *vs* 1.3 (1–3) repectively for sedation.

Requirements for intraoperative propofol are presented in table 2. Propofol consumption was reduced by 14.5% in group C in comparison with group H ($P = 0.041$). The number of additional propofol boluses used for the maintenance of anaesthesia was reduced by 52.2% in group C in comparison with group H ($P = 0.013$). Patients in group C spent more time at the lowest maintenance infusion rate of 4 mg kg^{-1} h^{-1} ($P = 0.017$) and had a lower final infusion rate ($P = 0.0062$). The number of propofol boluses for induction of anaesthesia did not differ between the two groups.

Heart rate did not differ between groups C and H on arrival in the operating room (table 3), whereas mean arterial pressure was significantly reduced in group C ($P = 0.027$). After induction of anaesthesia, heart rate and mean arterial pressure did not differ between the two groups. In contrast, they were significantly reduced in group C after intubation ($P = 0.0036$ and 0.0053 respectively). During anaesthesia, patients receiving clonidine exhibited a significantly lower heart rate ($P = 0.041$) and mean arterial pressure ($P = 0.0019$) than those in the group H. No patient had hypotension or symptomatic bradycardia requiring ephedrine administration.

Time to response to verbal command (14.2 (5–25) min in group H and 15.7 (5–30) min in group C), extubation (15.9 (9–27) min and 16.7 (5–33) min respectively) and correct recall of date of birth (23.8 (10–55) min and 22.5 (9–46) min respectively) from the end of propofol infusion and time spent in the recovery room (91.9 (60–132) min and 107.8 (45–200) min respectively) did not differ between the two groups.

Table 3 Haemodynamic data (mean (SD)), BP denotes arterial pressure. $*P<0.05$ and $**P<0.01$ compared with the hydroxyzine group

	BP (mm Hg)		Heart rate (beats min^{-1})	
	Hydroxyzine group	Clonidine group	Hydroxyzine group	Clonidine group
On arrival in the operating room	84 (9)	76 (8)*	64 (13)	61 (11)
After induction of anaesthesia	76 (14)	70 (9)	60 (9)	56 (9)
After intubation	89 (13)	74 (10)**	69 (13)	55 (8)**
Mean during anaesthesia	87 (9)	76 (5)**	62 (7)	55 (7)*

Discussion

The present study shows that, in ASA I patients, premedication with a low dose of oral clonidine significantly reduces propofol requirements in comparison with hydroxyzine. Moreover, use of clonidine preserves intraoperative haemodynamic stability and does not delay recovery.

These data confirm and extend the results obtained by Richards and colleagues who reported reduced motor responses to skin incision during propofol–alfentanil anaesthesia in a small subgroup of eight patients given larger doses of clonidine doses before operation.[14] These previous results suggested that a deeper level of anaesthesia could be achieved after use of clonidine as an agent for premedication.

We used monitoring of clinical haemodynamic variables to assess indirectly the depth of anaesthesia. More accurate monitors of depth of anaesthesia could have been used, such as the bispectral index, which is strongly correlated with blood concentration of propofol, state of consciousness and explicit recall.[17] Nevertheless, availability of the bispectral index is limited and haemodynamic variables remain the most routinely used indices of depth of anaesthesia in clinical practice. Also, we used a manually controlled system for propofol infusion. Computer-controlled infusion devices programmed using pharmacokinetic models are an attractive alternative for i.v. delivery of propofol. Although we did not use this paradigm for maintenance of anaesthesia, the algorithm for adapting the infusion regimen during surgery was based on strictly defined criteria.

We observed a reduction in propofol requirements in the clonidine group during maintenance of anaesthesia. However, the propofol dose requirements for inducing anaesthesia were not different between the clonidine and the hydroxyzine groups. This is different from the findings of Richards and colleagues[14] and those reported for other i.v. induction agents such as barbiturates.[5 9] This could be related to the high loading dose of propofol (2.5 mg kg^{-1}) we used, which could have masked an effect on induction requirements.

The potentially beneficial anaesthetic-sparing effect of $alpha_2$-agonists may be negated by bradycardia and hypotension. I.v. fluid loading or the use of catecholamines to maintain heart rate and arterial pressure have been used after use of dexmedetomidine in elderly patients[15] and in patients undergoing vascular surgery.[18 19] In the present study, patients receiving clonidine exhibited a significant reduction in intraoperative heart rate and mean arterial pressure but did not develop symptomatic bradycardia or hypotension requiring vasopressor therapy. This could be explained in part by the ASA I physical status of the patients. Also, all received a high volume of cristalloid infusion (10 ml kg^{-1}) during the first hour of anaesthesia. Nevertheless, these results may not apply to elderly patients, especially if they have cardiovascular disease.

The reduction in propofol dose requirements reported by Richards and colleagues[14] was associated with significant delay in recovery times. It was likely to be attributable to the use of a high dose of clonidine (8.5 μg kg^{-1}) in combination with a benzodiazepine. With the 5 μg kg^{-1} regimen used in our study, we failed to detect any delay in recovery from anaesthesia (power to detect a 50% increase in recovery time >80%). This is consistent with the data of Kumar and Ghignone, who independently reported a faster recovery in elderly patients undergoing intraocular surgery and premedicated with 5 μg kg^{-1} clonidine when compared with patients premedicated with diazepam.[20 21]

In summary, premedication with 5 μg kg^{-1} clonidine significantly reduced intraoperative propofol requirements in healthy subjects undergoing orthopaedic surgery without inducing adverse effects on recovery or haemodynamic stability.

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Administration of a crystalloid fluid preload does not prevent the decrease in arterial blood pressure after induction of anaesthesia with propofol and fentanyl

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Summary

Anaesthesia was induced in 58 women (ASA I or II) undergoing elective gynaecological procedures, using propofol 2.5 mg kg^{-1} and fentanyl 1.5 μg kg^{-1}. Patients were allocated to receive 20 ml kg^{-1} of crystalloid fluid preload over 20 min or to receive no fluids before induction of anaesthesia. A significant decrease in systolic arterial pressure (<75% of baseline value) occurred in both the fluid-loaded and the control groups, and was similar in both groups. Administration of a fluid preload did not attenuate the decrease in systolic arterial pressure after induction of anaesthesia with propofol and fentanyl. (*Br. J. Anaesth.* 1998; **80**: 737–741)

Keywords: anaesthetics i.v. propofol; complications hypotension; fluid balance fluid therapy

Propofol (2,6 diisopropylphenol) is a rapidly acting i.v. anaesthetic agent that has gained wide acceptance for the induction and maintenance of general anaesthesia. Propofol is ideal for short and ambulatory surgical procedures requiring general anaesthesia, as recovery is rapid with fewer unwanted side effects, such as drowsiness on recovery, disorientation and nausea, when compared with other agents such as thiopentone. The induction of general anaesthesia with propofol, however, has been associated with a decrease in systolic arterial blood pressure.[1–3] While this decrease in blood pressure is rarely clinically important in young and healthy individuals, this may not be the case in patients who are elderly, medically unwell or pregnant, in whom hypotension may critically reduce tissue perfusion and oxygenation.

The aim of the present study was to determine whether preloading patients with crystalloid fluid would prevent or attenuate this decrease in blood pressure.

Patients and methods

After obtaining approval from the regional ethics committee and informed consent we studied 58 women, ASA I or II, undergoing elective gynaecological procedures. Patients were allocated according to month of birth to receive 20 ml kg^{-1} of crystalloid fluid preload over 20 min (group F) or to receive no fluids before induction of anaesthesia (group NF). To achieve blinding, the fluid preload was given outside the operating theatre by one investigator, and the empty fluid bags replaced with fresh fluid bags. Thus all patients arrived in theatre with full fluid bags attached to the i.v. fluid administration sets, and the anaesthetist was unaware whether the patient had received a fluid preload. Exclusion criteria included a history of taking vasoactive medications, hypertension, cardiovascular disease and a body weight greater than 90 kg.

The patients received no premedication. In the anaesthetic room, i.v. access was established using local anaesthetic and a 16 gauge cannula in a superficial left forearm vein. Patients allocated to receive a fluid load were infused over 20 min with Hartmann's solution, 20 ml kg^{-1} warmed to 38°C. Patients in group NF received minimal fluids, to keep the vein open, until the end of the study, when fluid therapy was left to the discretion of the attending anaesthetist.

Blood pressure was measured using the Finapres (Ohmeda) automated continuous non-invasive blood pressure monitor. An appropriately sized cuff was applied to the right-hand forefinger and baseline blood pressure measurements were recorded. The monitor was serviced and calibrated twice by Ohmeda during the study.

Fentanyl 1.5 μg kg^{-1} was given 1 min before induction, and propofol 2.5 mg kg^{-1} injected over 20–30 s. After induction, haemodynamic variables were recorded at 15-s intervals for 4 min. End-tidal carbon dioxide was continuously monitored and the patient ventilated with 70% nitrous oxide and 30% oxygen via a face mask to maintain end tidal carbon dioxide at 34–40 mm Hg. Muscle relaxants were not given and no movement or surgical stimulation was permitted during the study period.

After completion of these measurements, the anaesthetic continued as normal with a further incremental dose of propofol or other agent given if clinically indicated. The treatment of hypotension was left to the discretion of the attending anaesthetist. No therapeutic interventions were required for any patient in this study.

The number of patients required for the study was calculated from an earlier study on the

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Table 1 Patient characteristics in the two study groups (mean (95% CI)). Group NF=no crystalloid fluid preload. Group F=crystalloid fluid preload with 20 ml kg^{-1} of Hartmann's solution

	Group NF (n=32)	Group F (n=26)
Age (yr)	33.3 (3.3)	31.3 (3.1)
Weight (kg)	63 (6.8)	62 (4.3)
Fasting time (h)	11.4 (1.5)	11.1 (1.5)
Fluid preload (ml)	0	1221.5 (86.7)

haemodynamic effects of propofol.[4] Using Altman's nomogram[5] for a study with a power of 0.90, 50 patients would be needed to detect a difference in mean arterial blood pressure of 10 mm Hg at the 0.05 level. Patient characteristics were analysed statistically using Student's unpaired t test. The haemodynamic data were analysed using ANOVA for repeated measures for differences between groups and for changes within groups. The method of summary measures as described by Matthews and colleagues[6] was used to compare haemodynamic variables at 1 and 4 min. Statistical analysis was performed using a package designed for personal computers (Number Cruncher Statistical System, JL Hintze, Kaysville, UT, USA). The data are presented as mean (95% confidence intervals).

Results

There were 26 patients in group F and 32 patients in group NF. The two groups were comparable with respect to age, weight and fasting times (table 1). The mean fluid load for group F was 1222 (87) ml. There were no statistical differences in baseline blood pressures between the groups.

Systolic arterial pressure (SAP) decreased significantly (P<0.001) in both groups after induction of anaesthesia. Blood pressures recorded at 4 min were 75% of baseline values in group NF and 74% of baseline values in group F. The SAP decreased from 132 mm Hg to 99 mm Hg (P<0.001) at 4 min and from 129 mm Hg to 96 mm Hg (P<0.001) at 4 min in groups NF and F respectively. The decrease in SAP over time was similar for both groups. There was no significant difference between the two groups (fig. 1). Decrease in mean arterial blood pressure (MAP) and diastolic blood pressure (DAP) was also compared. MAP and DAP were similar in both groups. There were no significant differences in MAP and DAP (fig. 2) between the two groups.

Baseline heart rates were similar in both groups. Initially heart rates increased in both groups, reaching a peak at 15 s. Heart rates recorded at 15 s from induction increased by 116% in group NF and

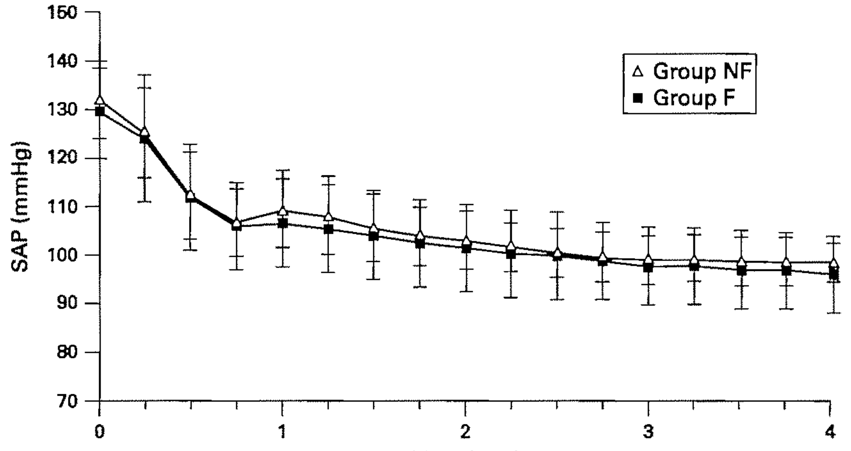

Figure 1 Changes in systolic arterial pressure (SAP) (mean (95% CI)) after propofol administration in groups NF (no fluid preload) and F (fluid preload). Values at 0 min indicate baseline blood pressures.

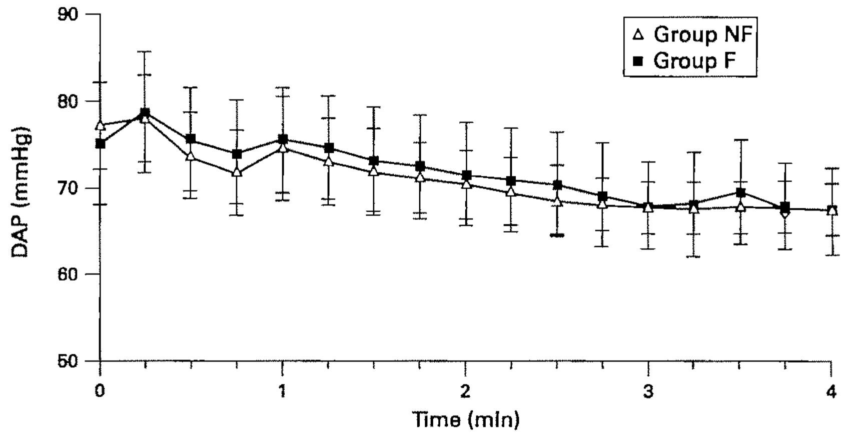

Figure 2 Changes in systolic arterial pressure (DAP) (mean (95% CI)) after propofol administration in groups NF (no fluid preload) and F (fluid preload). Values at 0 min indicate baseline blood pressures.

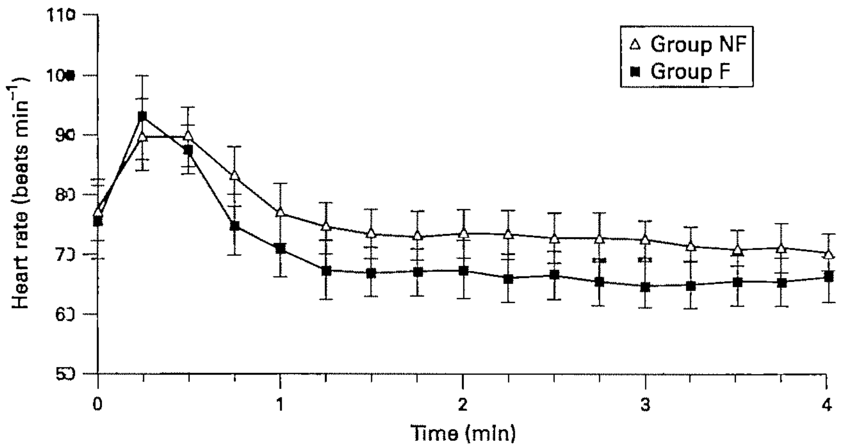

Figure 3 Changes in heart rate (mean (95% CI)) after propofol administration in groups NF (no fluid preload) and F (fluid preload). Values at 0 min indicate baseline heart rate. Heart rates in group F are less than those in group NF from 30 s to 4 min ($P<0.001$)

120% in group F. This corresponded to an increase of heart rate from 77 to 90 beats min^{-1} ($P<0.01$) and 75 to 92 beats min^{-1} ($P<0.01$) at 15 s in the groups NF and F respectively. After the initial increase, heart rate gradually declined to a level below baseline. Heart rates recorded at 4 min from induction were 91% of baseline values in group NF and 88% of baseline values in group F. Overall the heart rate decreased from 77 to 70 beats min^{-1} ($P<0.01$) and 75 to 66 beats min^{-1} ($P<0.01$) at 4 min in groups NF and F respectively. From 30 s to 4 min after propofol was given, the heart rate in group F was significantly less than the heart rate in group NF ($P<0.001$). The average difference between mean heart rate in both groups was 6.4 beats min^{-1} (fig. 3).

Discussion

This study demonstrates that the infusion of 20 ml kg^{-1} of crystalloid preload does not prevent or attenuate the decrease in blood pressure after induction of anaesthesia with propofol and fentanyl. For the purposes of this study we defined clinically significant hypotension as a decrease in blood pressure of greater than 20% below baseline measurements.

Clinically, hypotension becomes important when end-organ blood flow is reduced. The degree of hypotension required to reduce end-organ blood flow will depend on the health of the patient and the ability of the vascular beds of individual organs to autoregulate blood flow. In a young, fit individual, during deliberate hypotensive anaesthesia, a mean arterial blood pressure as low as 50–65 mm Hg appears to be tolerated,[7] but at this blood pressure renal blood flow is significantly reduced. Renal blood flow is impaired when the mean arterial blood pressure falls below 80 mm Hg.[8] An elderly, pregnant or medically compromised patient will not tolerate hypotension to the same degree as a young, healthy patient and it is difficult to predict the level at which end-organ blood flow is reduced. When considering these factors a decrease in arterial blood pressure of greater than 20% below baseline indicates a clinically significant fall in arterial blood pressure, but is unlikely to result in end-organ hypoperfusion, particularly in the healthy patient.[9] The Finapres continuous non-invasive blood pressure monitor was used to measure arterial blood pressure. This useful instrument allows continuous measurement of arterial blood pressure without the discomfort and potential complications of arterial catheter placement. The Finapres has been extensively evaluated and compared with invasive arterial pressure monitoring. While recordings made using the Finapres correlate well with invasive arterial pressure monitoring,[10 11] discrepancies have been reported between the two methods of blood pressure measurement, particularly when arterial blood pressure is high.[12]

Fentanyl was used to supplement induction of anaesthesia with propofol. The cardiovascular effects of low-dose fentanyl are minimal.[13] In combination with propofol there is some evidence that the addition of low-dose fentanyl may accentuate hypotension and cause a slower heart rate when compared with that in patients who have received propofol only for induction of anaesthesia.[14] In this study the haemodynamic effects of fentanyl would apply equally to both groups. Similarly, the use of nitrous oxide was required to ensure anaesthesia during the duration of the study. While nitrous oxide may influence the haemodynamic variables, this effect would also apply to both groups equally.

Hypotension after induction of anaesthesia with propofol is well recognized. This observation was supported by the present study and occurred equally in both groups. While fluid preloading did not prevent hypotension it did affect the cardiovascular response to propofol induction of anaesthesia, reducing the overall heart rate in the fluid-preloaded group. However, fluid preloading did not reduce the initial tachycardia seen in both groups immediately after propofol administration. The mechanism of propofol-induced hypotension is unresolved. While many studies have demonstrated a significant decrease in systemic vascular resistance[15 16] that would account for the decrease in arterial blood pressure, the effect of propofol on the myocardium is more controversial. Some studies suggest that propofol causes a significant reduction in contractility[17] while others demonstrate only minimal depression of contractility.[18] Other studies attribute the decrease in blood pressure to both a decrease in systemic vascular resistance and a decrease in myocardial contractility.[4 19]

The use of a crystalloid fluid preload to prevent hypotension after induction of anaesthesia with propofol has not been extensively evaluated. Several mechanisms may be postulated to explain the failure of fluid loading to attenuate hypotension after the induction of anaesthesia with propofol. The crystalloid fluid administered may be rapidly distributed into the interstitial and intracellular spaces with only a little remaining in the systemic circulation. Previous studies have suggested that the increase in pulmonary artery pressure after rapid infusions of crystalloid may be quite transient, with modest increases in pulmonary pressures returning to baseline values within 15–20 min.[20] Measurement of central venous or pulmonary artery pressures would help further to define the degree of fluid redistribution. Colloidal solutions may be more effective in attenuating the decrease in blood pressure because a greater proportion is retained in the intravascular space. We propose that an alternative explanation may be found in the pharmacodynamic effects of propofol. If the predominant mechanism for hypotension is loss of arteriolar tone and reduced systemic vascular resistance, then fluid administration would be less effective in reducing hypotension than if the predominant mechanism is reduced myocardial contractility or venous dilation. Further investigation with monitoring of central venous pressure and cardiac output would help to define these cardiovascular changes.

The use of a fluid load to treat hypotension during anaesthesia has been well established. In the healthy patient, fluid preloading is associated with minimal risk. In the elderly or medically compromised patient, fluid preloading requires cautious administration to avoid complications such as pulmonary oedema. The healthy obstetric patient, however, is able to tolerate a fluid load, and it is generally believed that fluid preloading is beneficial for these patients under some circumstances. Fluid preloading is practised routinely in many obstetric units to prevent hypotension before central neuraxial block.[21] Recent studies have questioned the value of this practice.[22 23]

Heart rate increased immediately after propofol injection. This is best explained by the arterial baroreceptor response to arterial hypotension. Subsequently the baroreceptor response appears to be inhibited, with heart rate slowing to below preinduction levels. Depression of the baroreceptor response has been documented in previous studies.[1 2] These studies have demonstrated similar changes in heart rate over time, after induction of anaesthesia with propofol. In the fluid-loaded group heart rate was lower when compared with that in the control group. It is possible that fluid loading produces an increase in myocardial preload, leading to an increased stroke volume and therefore maintains cardiac output at a lower heart rate without increasing blood pressure. This supports our hypothesis that decreased systemic vascular resistance is the predominant mechanism for hypotension following propofol administration. Further studies are required fully to evaluate the mechanisms causing hypotension after propofol administration.

In conclusion we found that the i.v. administration of crystalloid fluid does not prevent the decrease in arterial blood pressure after induction of anaesthesia with propofol and fentanyl. This practice cannot be recommended as a satisfactory technique to prevent hypotension following induction of general anaesthesia with propofol.

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Postoperative hypoxaemia: continuous extradural infusion of bupivacaine and morphine *vs* patient-controlled analgesia with intravenous morphine

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Summary

We carried out a randomized prospective study in 60 patients who had undergone major abdominal surgery for cancer. For postoperative pain control, 30 patients received continuous extradural infusion of 0.125% bupivacaine 12.5 mg h^{-1} and morphine 0.25 mg h^{-1} (EXI group) and 30 received patient-controlled analgesia (PCA) with intravenous morphine (1 mg bolus, 5-min lock-out and maximum dose 20 mg $4h^{-1}$). Both groups had general anaesthesia. The two groups were compared for postoperative pain scores, satisfaction, sedation and oxygen saturation. Oxygen saturation was recorded continuously the night before surgery and for two consecutive postoperative nights. Episodes of moderate desaturation (90%> Sp_{O_2} 85%) were more frequent in the EXI group than in the PCA group (P<0.05). Pain scores were lower in the EXI group compared with the PCA group at rest and while coughing (P<0.05). No significant difference was found for patient sedation and satisfaction. (*Br. J. Anaesth.* 1998; **80**: 742–747)

Keywords: analgesia extradural; analgesia patient-controlled; analgesics nonopioid bupivacaine; analgesics opioid morphine; complications hypoxaemia; monitoring oxygen; surgery abdominal

In recent years, attention has been devoted to improving postoperative analgesia.[1] However, controversies persist regarding the use of relatively invasive techniques. One disturbing consequence of analgesic regimens involving opioids, whatever the route of administration, is the potential for respiratory depression,[2] especially on general surgical wards.[3] Although the spinal route of administration has been an area of special concern, the more traditional parenteral route is not without risk.[2] Many articles encourage anaesthetists to be more attentive to this aspect of postoperative management.[4]

Infusing a mixture of local anaesthetic and opioids into the extradural space makes it possible to reduce the total amount of each drug the patient receives. Unwanted side effects are thus minimized, while achieving better analgesia and postoperative respiratory function.[5-7] However, the respiratory advantages of such a postoperative regimen are uncertain.

Patient-controlled analgesia (PCA) allows patients to choose the most appropriate dose themselves. A sedated patient is less likely to press the button on the PCA pump, thus indirectly reducing the dose of opioid and the risk of postoperative hypoxaemia.[8] By using PCA, by either the intravenous or extradural route, it should be possible to improve analgesia and reduce the risk of respiratory depression. We have already studied patients receiving either parenteral morphine or continuous extradural infusion of bupivacaine and morphine after major abdominal surgery.[7] Arterial oxygen saturation Sp_{O_2} was continuously measured during the first postoperative night. The number of patients with nasal oxygen and with episodic arterial haemoglobin desaturation was slightly lower in the extradural group than in the parenteral group. This finding was difficult to interpret, however, as oxygen therapy exerts variable effects on the correction of episodic arterial haemoglobin desaturation. Several studies have evaluated the occurrence of desaturation after different types of analgesia,[9-14] but in none has arterial haemogloblin oxygen saturation been analysed continuously for 2 nights after major abdominal surgery. Prolonged monitoring is important, because desaturation episodes may be worse during the second postoperative night.[15]

Therefore we carried out a prospective randomized study to compare postoperative arterial haemoglobin saturation, pain relief and sedation in two groups of patients receiving postoperatively either PCA with intravenous morphine or continuous extradural infusion of bupivacaine and morphine while breathing room air.

Patients and methods

The study was approved by the local scientific committee on ethical clinical research and informed written consent obtained from each patient. Sixty adults (ASA I or II, age 18–70 yr) due to undergo major abdominal surgery for cancer (midline or bi-subcostal incision) were randomized for postoperative pain relief to receive either an extradural infusion (EXI, n=30) or parenteral patient-controlled analgesia (PCA, n=30). Exclusion criteria were: obesity,

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Table 1 Patient characteristics and duration of surgery (mean (SD)). EXI=extradural infusion; PCA=patient-controlled analgesia. No significant differences

	EXI group (n=28)	PCA group (n=29)
Age (yr)	60 (10)	56 (11)
Weight (kg)	69 (13)	73 (10)
Height (cm)	170 (10)	171 (11)
Sex (M/F)	10/18	10/19
Duration of surgery (min)	195 (57)	204 (80)

Table 2 Surgery. EXI=extradural infusion; PCA=patient-controlled analgesia. No significant differences

Type of surgery	EXI group (n=28)	PCA group (n=29)
Pelvectomy	6	6
Hysterectomy with pelvic and lumbo-aortic lymphadenectomy	6	4
Hepatectomy	5	4
Colectomy	3	5
Gastrectomy	5	5
Splenectomy	1	1
Laparotomy	2	4

pulmonary disease, heavy smoking (more than 20 pack-years) and contraindication to extradural analgesia.

Oxygen saturation was monitored the night before surgery and during the first 2 nights after surgery from 19:00 to 07:30. Premedication was with alprazolam 0.5 mg. General anaesthesia was induced with etomidate 0.2–0.3 mg kg^{-1}, fentanyl 1–2 μg kg^{-1} and vecuronium 0.1 mg kg^{-1}, and maintained with nitrous oxide/oxygen (0.55/0.45), 1–1.2% isoflurane, fentanyl 1 μg kg^{-1} and vecuronium 0.02 mg kg^{-1}. Tracheal extubation was carried out at the end of the procedure after antagonization of neuromuscular block.

Before surgery, the EXI group received an explanation of extradural analgesia and instruction on how to use the visual analogue scale (VAS). A thoracic extradural catheter was inserted at the T9–T11 level before induction of general anaesthesia. Lidocaine 2% with epinephrine 1:200–000 (3 ml) was used as a test-dose. The extradural catheter was not used during surgery. After completion of surgery, in the recovery room, a bolus dose of 0.125% bupivacaine with morphine 0.25 mg ml^{-1} was injected into the catheter to achieve a bilateral and symmetrical T6 sensory block. Simultaneously, an extradural infusion of the same mixture was started at the rate of 10 ml h^{-1}. The infusion rate was reduced when motor block was achieved. No supplementary analgesic was given during the first 48 h; if this was needed, the patient was withdrawn from the study.

All patients in the PCA group were familiarized with the PCA pump and instructed on how to use the VAS. In the recovery room, i.v. morphine was titrated in boluses of 3 mg every 10 min to achieve adequate pain relief by a four-point verbal scale (no pain; moderate pain; severe pain; very severe pain). No pain and moderate pain were considered to indicate

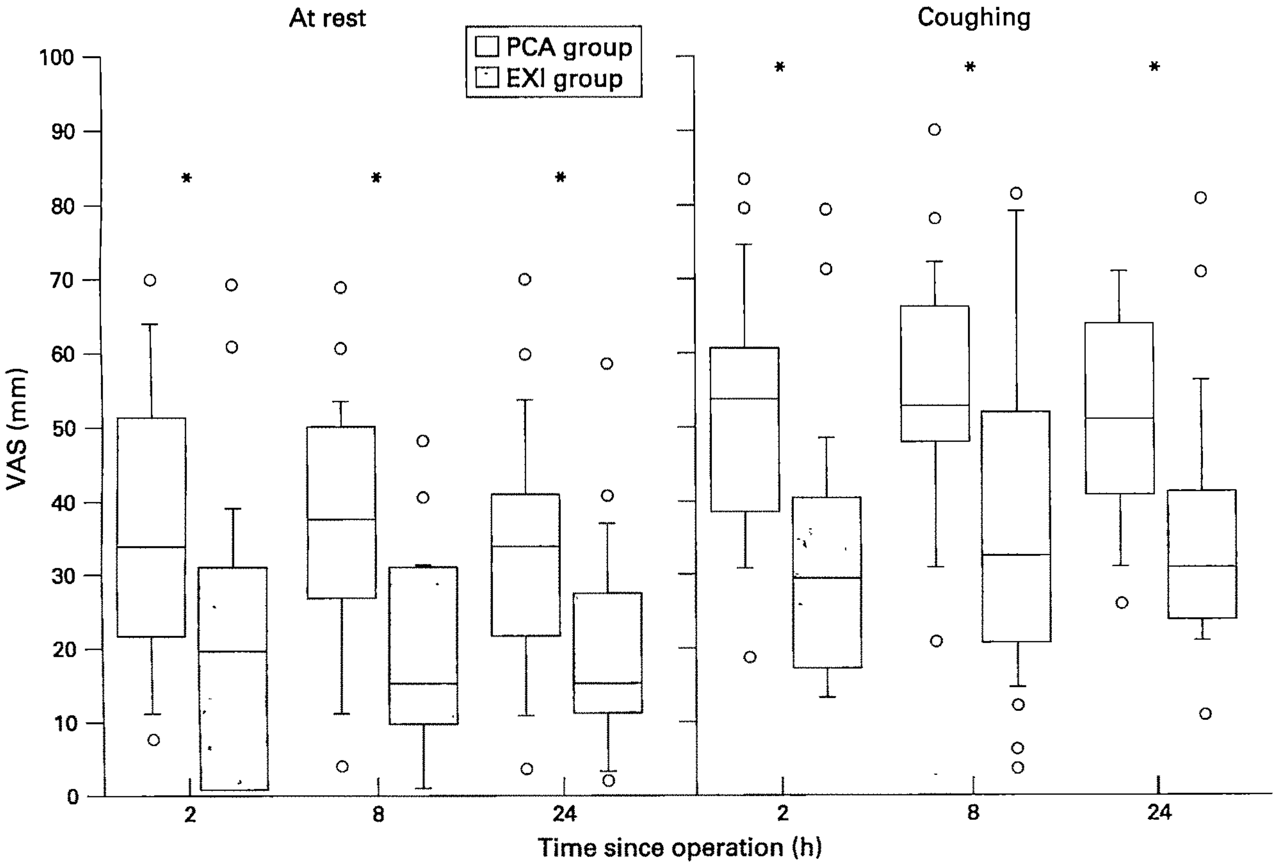

Figure 1—Pain scores (VAS) at 2, 8 and 24 h postoperatively at rest and during a cough. EXI=extradural infusion; PCA=patient-controlled analgesia. Boxes represent interquartile range, error bars are the 10th and 90th percentiles, horizontal lines in the boxes represent median values, open circles represent values outside 10th and 90th percentiles. Pain scores are significantly higher in the PCA group compared with the EXI group; *P<0.05.

Table 3 Patient satisfaction. EXI=extradural infusion; PCA=patient-controlled analgesia. No significant differences

Satisfaction	EXI group (n=28) Patients (%)	PCA group (n=29) Patients (%)
Very satisfied	28	26
Satisfied	28	44
Mildly satisfied	33	4
Poorly satisfied	11	26

Table 4 Sedation. EXI=extradural infusion; PCA=patient-controlled analgesia. No significant differences

Sedation scale	EXI group (n=28) Patients (%)	PCA group (n=29) Patients (%)
Awake	33	22
Sleepy but easily wakeable	62	78
Sleepy but hardly wakeable	5	0
Very sleepy	0	0

Table 5 Morphine usage for the first 48 h after operation. Values are means (SD). EXI=extradural infusion; PCA=patient-controlled analgesia. *P<0.05 compared with EXI group; **P<0.05 compared with first postoperative night

Morphine (mg)	EXI group (n=28)	PCA group (n=29)
During the first night	2.9 (1.2)	18.0 (8.1)*
During the first 24 h	5.9 (2.3)	40.6 (17.5)*
During the second night	2.9 (1.1)	12.1 (5.9)**
During the first 48 h	11.9 (3.0)	65.8 (24.3)*

adequate pain relief, and severe and very severe pain inadequate relief. The PCA pump was programmed to deliver a morphine bolus of 1 mg with a 5-min lock-out and a maximum dose of 20 mg 4 h^{-1}. No background infusion of opioids was used and, as in the EXI group, no supplementary analgesia was given.

Postoperative pain was quantified using a 10-point VAS at 2 h, 8 h and 24 h at rest and while coughing. Sedation was noted by the same physician using a sedation scale (awake; sleepy but easily wakeable; sleepy and hardly wakeable; very sleepy). Patient satisfaction was graded as very satisfied, satisfied, mildly satisfied or poorly satisfied.

Oxygen saturation Sp_{O_2} was assessed using a finger probe with a pulse oximeter (Nellcor N200, Hayward Ca.) able to store Sp_{O_2} readings in a compressed database. Every 5-s period was averaged by the oximeter and stored in the 12-h memory set. For off-line analysis, the raw Sp_{O_2} data were transferred via the RS232 output channel of the monitor using a specially designed program (courtesy of Mr Gauthé, CDC, Foch, Suresnes, France).[16] The computer rejected Sp_{O_2} artefacts. The Sp_{O_2} reading was considered an artefact if it reached zero, or if it decreased by more than 25% from one 5-s average value to another. Rejected data points were replaced by blank values to avoid altering the recording time scale. We used the modal Sp_{O_2} (the percentage of time spent at a given Sp_{O_2}, as it has been reported to be an adequate method for assessing nocturnal hypoxaemia.[17] With this method, there is a strong correlation between the number of desaturation dips and the percentage of time spent at certain Sp_{O_2} values. Saturation values were assessed as normal $Sp_{O_2} \geq 95\%$, mild desaturation ($95 > Sp_{O_2} \geq 90\%$), moderate desaturation ($90\% > Sp_{O_2} \geq 85\%$) and severe desaturation ($85\% > Sp_{O_2} \geq 80\%$). All patients were breathing room air during pulse oximetry. If Sp_{O_2} dropped below 85% and remained there for >2 min, nasal oxygen was administered and the patient withdrawn from the study.

Statistical analysis was done using Sigmastat Jandel statistical software. A P value <0.05 was considered statistically significant. Patient characteristics were compared using a Student's t-test. A Mann–Whitney rank sum test was used to compare duration of surgery, morphine consumption, perioperative saturation and pain scores in both groups. Friedman's one-way repeated measure of ANOVA on ranks and multiple comparison's test and Dunnett's method were used to compare the perioperative saturation within each group. The chi-square test was used to compare sex distribution, satisfaction, sedation and type of surgery.

Results

A total of 60 patients was enrolled in the study (30 in each group). Three patients (two in the EXI group and one in the PCA group) were excluded because of severe oxygen desaturation (saturation of <85% lasting for >2 min, necessitating oxygen supplementation).

Patient 1 (EXI group, colonic resection, age 65 yr) developed interstitial pulmonary oedema without infection during the first postoperative night. He was hypoxaemic, and chest x-ray showed bilateral infiltrates without evidence of localized consolidation. The desaturation episode responded readily to oxygen therapy and diuretic treatment. Patient 2 (EXI group, colonic surgery, age 70 yr) developed pneumonia 36 h after surgery; she was transferred to the ICU and mechanically ventilated for 3 days. Patient 3 (PCA group, hysterectomy with pelvic and lomboaortic lymphadenectomy, age 58) had prolonged desaturation during the first postoperative night and was very sedated. We found no specific cause for these symptoms. Nasal oxygen was stopped the following morning and desaturation did not recur.

Fifty-seven patients were analysed. No patient was excluded because of inadequate analgesia. There was no statistical difference between the two groups with respect to age, weight, height, sex distribution or duration or type of surgery (tables 1 and 2).

VAS scores were significantly lower at 2, 8, and 24 h postoperatively in the EXI group at rest and while coughing (fig. 1) (P<0.05). The percentage of satisfied patients was higher in the PCA group, but the difference was not statistically significant (table 3). There were no differences in sedation scores (table 4).

For three patients in the EXI group, the extradural infusion rate was decreased from 10 ml h^{-1} to 8 ml h^{-1} because of motor block grade 2 (modified 4-grade Bromage scale). Significantly more morphine was used in the PCA group than in the EXI group (table 5) (P<0.05). In the PCA group, the dose of morphine was significantly lower during the second night compared with the first night (table 5) (P<0.05).

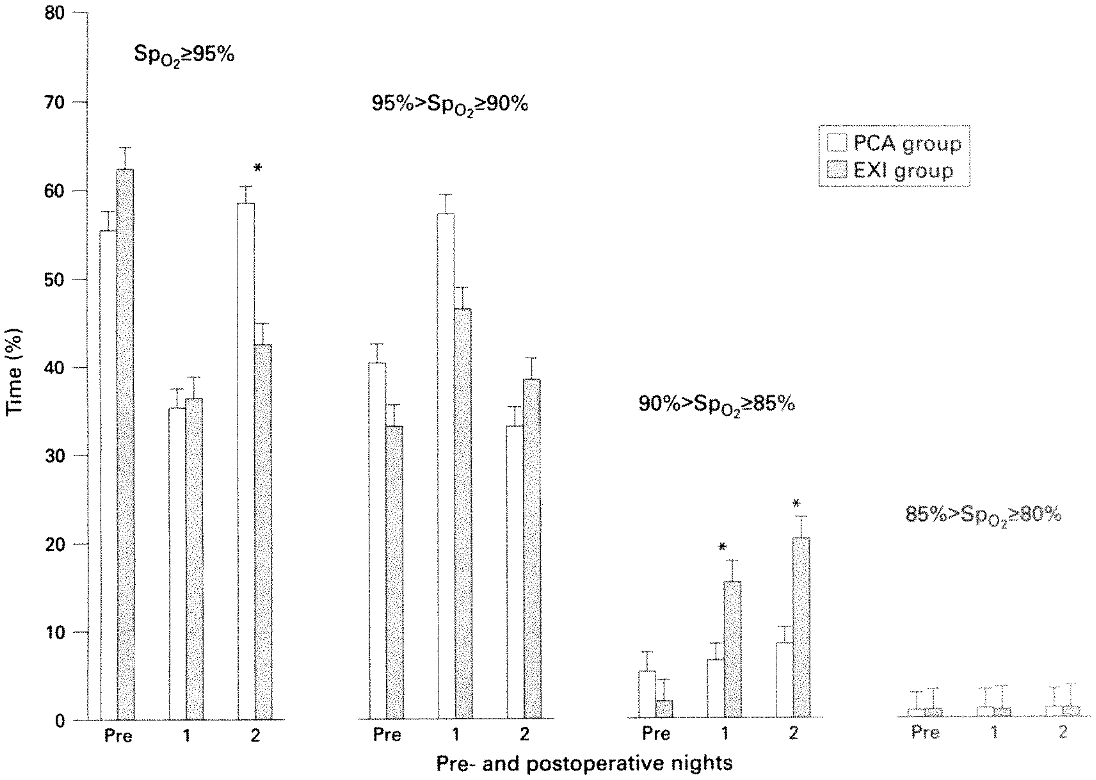

Figure 2 Percentage of time spent at different level of oxygen saturation. Values are mean (SE). EXI=extradural infusion; PCA=patient-controlled analgesia.

No statistical difference was found between groups in the time spent with an $Sp_{O_2} \geq 95\%$ during the preoperative night nor during the first postoperative night. Within each group, the percentage of time with an $Sp_{O_2} \geq 95\%$ during the first postoperative night was significantly less than during the preoperative night. During the second postoperative night patients in the EXI group spent significantly less time at this saturation compared with those in the PCA group (fig. 2) ($P<0.05$).

There were no significant differences between groups or within groups in the number of desaturation episodes (90–95%) during the first postoperative night (fig. 2).

Episodes of moderate desaturation (85–90%) occurred in both groups during the preoperative and the first and second postoperative nights (fig. 2). Moderate desaturation was significantly more frequent within the EXI group compared with the PCA group during the first and second postoperative night ($P<0.05$). No difference was found between the first and second postoperative night in either group.

There were no significant differences between or within groups with respect to time spent with saturations of 80–85% (fig. 2).

Discussion

In this study, moderate postoperative arterial haemoglobin oxygen desaturation was more frequent among patients receiving extradural analgesia compared with those receiving patient-controlled analgesia after major abdominal surgery. Pain relief was significantly superior in the extradural analgesia group receiving continuous infusion of bupivacaine and morphine, compared with that in the patient-controlled analgesia group receiving morphine alone. However, no difference was found in sedation and satisfaction.

This prospective randomized study was not double-blinded, and the results could have been confounded by observer bias. However, the first purpose of our study was to measure physiological variables and the data were collected and analysed by computer. Investigators applied strict, predetermined criteria. For instance, if Sp_{O_2} dropped below 85% and remained there for >2 min, nasal oxygen was given and the patient was withdrawn from the study. Only two patients in the extradural group and one patient in the PCA group were excluded, so it is unlikley that bias influenced our results.

The site and size of abdominal incision, and diaphragmatic dysfunction, are important factors in the pathogenesis of postoperative hypoxaemia.[15 18 19] In the present study, all patients had major abdominal surgery for cancer with a mean duration of 3 h. Except for the patients who underwent hepatectomy (four patients in each group) via a bi-subcostal incision, all patients had large median incisions above and below the umbilicus. Therefore the two groups had a similar risk of postoperative respiratory complications.

Regarding pain relief, our results are comparable with those of other studies, and confirm superior pain relief is obtained with extradural analgesia compared with parenteral opioid analgesia.[4 6 7 9 10] However, we found no difference in satisfaction although there was a slight trend for more patients in the PCA group to be satisfied. Continuous extradural analgesia with a combination of local anaesthetics and opioids provides sustained pain relief,[20-22] but carries a risk of late respiratory depression because of systemic or CSF absorption of opioids.[23 24] The incidence of this complication is low (0.09–0.2%) but may occur even with hydrosoluble or liposoluble opioids.[23-25]

Several studies have reported the incidence of desaturation after various types of analgesia. Hypoxaemia occurred in all groups, although extradural analgesia tends to cause longer periods of desaturation.[9–14] Although these studies focused on lower abdominal surgery, and often pulse oximetry was monitored over only a 24-h postoperative period, the percentage of time spent with moderate and profound desaturation is comparable with our results. Prolonged monitoring is important because hypoxaemia may be worse on the second postoperative night and can last for up to 5 days.[15 26 27] However, we did not find in the extradural group that moderate desaturation was worse during the second night compared with the first night. We did not specify minimum periods of hypoxaemia. For instance, periods in excess of 6 min h^{-1} at a defined Sp_{O_2} value[10] were not used in this study. However, patients in the extradural group spent more than 10% of the time (or more than 6 min h^{-1}) with moderate desaturation. Hypoxaemic episodes may cause myocardial ischaemia or necrosis[28] but the minimum duration of desaturation that causes morbidity is not well established, as data are often expressed as cumulative episodes over 1 h.[19 29]

After surgery, episodic hypoxaemia may be related to sleep pattern disturbance and occurs more often during rapid-eye-movement (REM) sleep.[30–32] While general anaesthesia has minimal effect on REM sleep,[33] postoperative pain might contribute to disturbances in sleep pattern.[34 35] Also, during sleep or heavy sedation, tonic and phasic activity of all respiratory musculature is decreased, particularly that of the upper airway musculature, which can lead to obstructive apnoea and desaturation.[2] In the present study, one possible explanation for longer episodes of desaturation within the extradural group is the faster re-establishment of REM sleep, with an increase of sleep depth related to the quality of analgesia. Finally, the decrease of morphine consumption over time in the PCA group (table 5) may also explain the difference in desaturation episodes between the two groups.

The reliability of pulse oximetry of the upper limb can also be affected by extradural analgesia. Peduto and colleagues[36] noticed a progressive decrease in Sp_{O_2} values recorded in the hand (sympathetically unaffected) *vs* those in the foot, which was probably related to compensatory vasoconstriction that counterbalances lumbar sympathetic block. This phenomenon could also affect our data. However, Petudo's study concerned extradural anaesthesia in the operating room over a 30-min period. The haemodynamic status of the patients was stable, but only skin temperature was monitored and central body temperature was not controlled. Because the local anaesthetic dose differs, extradural anaesthesia blocks efferent sympathetic drive more efficiently than does extradural analgesia.[21] Therefore, observations during anaesthesia may differ from those during postoperative analgesia. This also does not explain why patients in the EXI group spent less time at saturation levels $\geqslant$95% only during the second night. Finally, other authors who have studied extradural morphine and applied the oximeter sensor to the patient's toe reported similar results to ours.[11 12]

Prophylactic oxygen therapy increases mean oxygen saturation, but does not eliminate the occurrence of sudden episodes of desaturation.[37] Therefore, low-flow oxygen therapy may not be effective in improving oxygenation because of the discrepancy between partial inspired oxygen pressure (F_{IO_2}) and partial arterial oxygen pressure (Pa_{O_2}) in the presence of ventilation/perfusion mismatching after abdominal surgery. A higher F_{IO_2} may be necessary to obtain clinically acceptable Pa_{O_2}.[38]

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Patient-maintained analgesia with target-controlled alfentanil infusion after cardiac surgery: a comparison with morphine PCA

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Summary

The performance of a patient-demand, target-controlled alfentanil infusion system was compared with that of a traditional morphine patient-controlled analgesia (PCA) pump in 120 adult patients after cardiac surgery. Patients were randomized to one of the two PCA systems for their postoperative analgesia in the intensive care unit and pain, nausea and sedation scores were recorded every 4 h for the first 24 h. Episodes of hypoxaemia, myocardial ischaemia and haemodynamic instability were also recorded. In patients using the alfentanil system the overall median visual analogue pain score was 2.3 (95% CI 2.3–2.8) compared with 3.0 (95% CI 2.7–3.2) in those using morphine PCA ($P<0.05$), but both systems delivered high-quality analgesia. The two groups did not differ with respect to the overall sedation scores, the frequency of postoperative nausea and vomiting, haemodynamic instability, myocardial ischaemia or hypoxaemia. (*Br. J. Anaesth.* 1998; **80**: 748–751)

Keywords: analgesia; patient-controlled target-controlled infusion; analgesics alfentanil morphine; surgery cardiac; pain postoperative

Postoperative pain may be managed poorly after cardiac surgery.[1] This can contribute significantly to increased morbidity and mortality, because the haemodynamic consequences of postoperative pain increase myocardial oxygen demand and make myocardial ischaemia more likely. Furthermore, several studies have shown that high-quality analgesia can reduce the severity of episodes of myocardial ischaemia[2 3] and facilitate early extubation with subsequent clearance of respiratory secretions after cardiac surgery.[3 4] Use of patient-controlled analgesia (PCA) has markedly improved the control of postoperative pain, but the technique has not been used widely in cardiac surgical patients. One study compared PCA using morphine with nurse-controlled morphine infusions after cardiac surgery but failed to show any difference in postoperative pain scores or extubation times.[5]

Morphine is the opioid analgesic most commonly used in PCA systems. When compared with alfentanil, it has a slower onset and offset of action after i.v. administration,[6] which may lead to a delayed onset of analgesia and subsequent oversedation. Alfentanil is more than 100 times more lipid soluble than morphine and at pH 7.4 is about 90% un-ionized, whereas morphine is about 20% un-ionized.[7] Therefore, alfentanil can diffuse from plasma to brain and back again more quickly than morphine, which explains its rapid onset and offset of analgesic activity. These physicochemical properties make alfentanil suitable for use in an pharmacokinetically based patient-controlled analgesia infusion system. The present study compared a target-controlled infusion (TCI) of alfentanil, which was controlled by the patient as patient-maintained analgesia (PMA), with a morphine PCA system in the first 24 h after cardiac surgery. The effect of these two PCA systems on postoperative pain, sedation and nausea and vomiting, and on myocardial ischaemia and haemodynamic instability, was evaluated.

Patients and methods

After obtaining hospital Ethics Committee approval and written informed consent, we studied 120 adult patients scheduled for elective cardiac bypass surgery. A closed-envelope technique was used to allocate patients randomly to receive a morphine PCA system (group M) or a patient-maintained, target controlled alfentanil infusion (group A) for their postoperative analgesia. Exclusion criteria were poor ventricular function, as defined by an ejection fraction of less than 40% measured during coronary angiography, and hepatic or renal impairment identified after routine preoperative screening of blood biochemistry.

All patients were shown the relevant PCA handset at the preoperative visit and instructed on its use the day before surgery. A standardized anaesthetic technique was used for all patients. Oral premedication consisted of temazepam 30 mg, metoclopramide 10 mg and ranitidine 150 mg given 2 h before operation. Anaesthesia was induced and maintained with target-controlled infusions (TCI) of propofol and alfentanil. The TCI infusion systems are computer-controlled pumps programmed with pharmacokinetic models for propofol and alfentanil.[8] When the age, sex and weight of the patient has been entered,

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Table 1 Sedation score used in this study

Score	Sedation	Nausea
0	Agitated	No nausea or vomiting
1	Awake	Nausea only
2	Roused by voice	Nausea and vomiting
3	Roused by touch	
4	Unrousable	
5	Muscle relaxants	
6	Sleeping	

Table 2 Patient characteristics and surgical data (mean (range)); no significant differences between groups. PMA=patient managed analgesia; PCA=patient controlled analgesia

	Alfentanil PMA patients	Morphine PCA patients
Age (yr)	58 (39–79)	61 (38–74)
Weight (kg)	76 (56–114)	76 (43–120)
Sex (M/F)	39/13	41/12
Cardiopulmonary bypass time (min)	79 (31–150)	86 (50–177)
Aortic crossclamp time (min)	51 (15–92)	55 (28–132)

the pumps can achieve and maintain any calculated plasma concentration selected. The lungs were ventilated with an air/oxygen mixture. Patients were cooled to 28°C during cardiopulmonary bypass and the selected target concentration of alfentanil was reduced. At the start of rewarming the TCI alfentanil infusion was stopped in group M patients, who received a 30 mg bolus dose of morphine followed by an infusion of 2 mg h^{-1} that was continued into the early postoperative period in the cardiac intensive care unit (CICU). Group A patients continued to receive the TCI alfentanil infusion and returned to the CICU after surgery with an initial predicted target concentration set at an appropriate level. The TCI propofol infusion was discontinued in both groups on arrival in the CICU. In both groups, patients were judged to be able to use a PCA handset when they opened their eyes and obeyed simple commands. At this point, the background infusion was stopped in group M patients and the PCA pump reprogrammed to deliver a 1 mg bolus with a 3-min lockout. In group A patients, a PCA handset was plugged into the alfentanil TCI system. When the patient successfully pushed the PCA button to request pain relief, the target concentration of alfentanil delivered was increased by 5 ng ml^{-1} with a lockout time of 2 min. If analgesia was not requested for 30 min, the target concentration was automatically reduced by 5 ng ml^{-1}. If the button was subsequently not pressed the target concentration was further reduced in steps of 5 ng ml^{-1} every 30 min for the first 4 h of use, every 45 min for the next 4 h and every 60 min thereafter. The system was programmed to deliver a minimum plasma concentration of 15 ng ml^{-1} and a maximum of 150 ng ml^{-1}.

Table 3 Surgical procedures. CABG=coronary artery bypass grafting; REDO=re-operation; AVR=aortic valve replacement; MVR=mitral valve replacement; ASD=atrial septal defect repair

	Alfentanil PMA patients	Morphine PCA patients
CABG	42	44
REDO CABG	1	0
AVR	6	5
MVR	1	1
AVR/MVR	0	1
CABG/AVR/MVR	1	0
CABG/AVR	0	1
CABG/MVR	0	1
ASD	1	0

The patients were extubated in the CICU when the following criteria were met: core temperature >36.5°C; patient obeys simple commands; haemodynamic stability (systolic arterial pressure >80 and <170 mm Hg, heart rate >50 and <120 beats min^{-1}); satisfactory arterial blood gases (Pa_{O_2}>12 kPa with FI_{O_2}<0.6; Pa_{CO_2}<7 kPa when breathing spontaneously); urine output >1 ml kg^{-1} min^{-1}; chest drain blood losses <30 ml h^{-1}. The elapsed time from CICU admission to extubation was recorded. Monitoring included 5-lead electrocardiography with continuous 3-lead ST segment analysis, intra-arterial pressure and continuous pulse oximetry. At 4-h intervals the nausea and sedation scores (table 1) and the visual analogue pain score (VAPS) were recorded and a blood gas sample drawn for measurement of Pa_{O_2} and Pa_{CO_2}. A 12-lead ECG was also taken every 4 h. Patients were observed for the first 24 h after operation. Visual analogue pain scores (VAPS) were recorded with the patients at rest, by CICU nursing staff who had been trained in the technique by one of the authors (MRC). The VAPS system had been explained to all patients on the day before surgery. For patients who were intubated it was possible to obtain a VAPS score if they were awake and able to obey simple commands, otherwise no score was recorded.

Myocardial ischaemia was defined as ST segment changes (elevation or depression) of more than 2 mm in any ECG lead, haemodynamic instability as a fluctuation in mean arterial pressure or heart rate by more than ± 30% in the first 24 h (± 30% compared with baseline values recorded after admission to CICU) and hypoxaemia as an oxygen saturation measured by pulse oximeter of <90%.

The assessors were not blinded because the two PCA systems were visually very different and cloaking them was impractical. At the end of the 24-hour study period, patients who had been randomized to the alfentanil PMA system received the morphine PCA pump for the next 2–3 days until simple oral analgesics were adequate.

All patients were visited by one of the authors on day 4 or 5 after surgery and asked to classify the quality of their initial postoperative analgesia as excellent, good, satisfactory or poor. They were also invited to comment on the patient-controlled analgesia system they had used.

Student's *t* tests were used to compare patient groups. We evaluated the VAPS by using the Mann–Whitney *U* test and comparing the 95% confidence intervals, as has been recommended.[9, 10] A chi-square test was used to compare nausea scores and Mann Whitney *U* tests for all other comparisons between the two groups, using Minitab for Windows software (version 9.2 running under Windows for Workgroups 3.11 on a Hi Grade LBC2 100 notebook computer). A $P<0.05$ was taken as statistically significant.

Results

One hundred and twenty patients were recruited into the study but 15 were withdrawn because of surgical

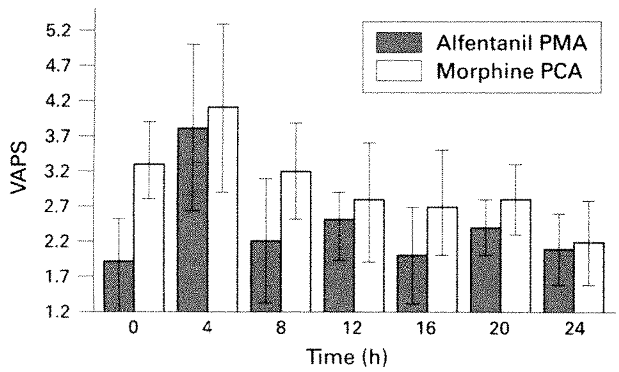

Figure 1 Postoperative pain in the two patient groups, measured at 4-h intervals by visual analogue pain scores (VAPS) (means, bars show 95% confidence intervals).

complications that required reoperation or violation of the study protocol. A total of 105 patients were studied. There were no differences betwen groups in patient characteristics (table 2). The surgical procedures are listed in Table 3.

Mean time to tracheal extubation in the alfentanil analgesia group was 288 min (95% confidence interval 218–358) compared with 411 min in the morphine group (95% CI 331–491) ($P<0.05$).

Median overall visual analogue pain scores for the 24-h study period were lower in patients using alfentanil patient-maintained analgesia, at 2.3 (95% CI 2.3–2.8) compared with 3.0 (95% CI 2.7–3.2) in the morphine group ($P<0.05$). However, there were no significant differences in the comparative VAPS at each of the 4-hourly assessments (fig. 1). Median 24-h consumption of alfentanil was 29.4 mg (range 11–59 mg, 95% CI 24–34 mg) and that of morphine was 45.5 mg (range 12–91 mg, 95% CI 39.9–51mg). Mean predicted alfentanil target concentration at admission to the CICU was 96 ng ml^{-1} (95% CI 89–103 ng ml^{-1}). However, the predicted alfentanil concentrations requested by individual patients ranged from 15 ng ml^{-1} to the maximum permitted value of 150 ng ml^{-1}.

There was no significant difference between the two groups in nausea or sedation scores. Twenty of 52 patients in the alfentanil and 24 of 53 in the morphine group had nausea scores greater than 1 in the first 24 h. Median sedation score in both groups was 2 (rousable to speech).

Myocardial ischaemic episodes were seen in 10 (19%) patients in the alfentanil group and 14 (26%) patients in the morphine group (no significant difference).

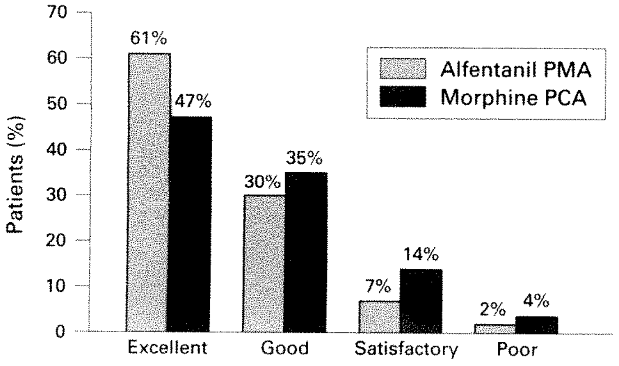

Figure 2 Overall patient satisfaction with postoperative analgesia.

Cardiovascular instability was found in 36% of patients in the alfentanil group (mean duration 61 min) compared with 41% of patients in the morphine group (mean duration 71 min). These differences were not statistically significant. One patient, who was in the alfentanil group, required a sodium nitroprusside infusion to control hypertension following an aortic valve replacement.

In the first 24 h after operation, oxygen saturations of <90% by pulse oximetry were recorded in nine (17%) of the alfentanil group (mean duration 21 min) and 14 (26%) patients in the morphine group (mean duration 39 min). These differences were not significant. There was no significant difference in the Pa_{CO_2} values from blood gases in the two patient groups, the mean values being 5.5 (SD 0.836) in the alfentanil group and 5.6 (SD 1.43) in the morphine group.

Ninety-one percent of patients who used the alfentanil PMA system rated their postoperative analgesia as excellent or good while the remaining 9% felt it was only satisfactory or poor. The corresponding figures in patients in the morphine group were 82% and 18%. However, these differences were not statistically significant (fig. 2). Alfentanil plasma concentrations requested by patients who rated their analgesia as excellent or good did not differ from those in the group rating their analgesia as satisfactory or poor.

Discussion

The pharmacokinetic and pharmacodynamic profile of alfentanil make it suitable for use in a patient-maintained TCI system. It has a rapid onset of action and short elimination half life and has been shown to provide good-quality analgesia when administered by TCI after major vascular surgery.[11] Morphine, which is the opioid most commonly used in PCA pumps in the UK, has a relatively slow onset of action and analgesia may be delayed.[6]

Use of both alfentanil target-controlled, patient-maintained analgesia and morphine bolus PCA resulted in good quality analgesia in patients after cardiac surgery. Lower pain scores were recorded in the patients who received alfentanil, but although statistically significant, this difference is probably not clinically significant. The median pain scores of 2.3 in the alfentanil PMA group and 3.0 in the morphine PCA group were within the "zone of analgesic success" of VAPS <3.0 postulated by Manthra.[9] The present results compare favourably with a previously reported median pain score of 4.0 after cardiac bypass surgery, when intravenous bolus doses of morphine were administered by nursing staff.[1]

In the present study, patients who received alfentanil were extubated significantly sooner than those in the morphine group. The clinical impression was that the alfentanil patients were less sedated, particularly in the first 12 h after surgery, but this was not substantiated after statistical analysis of the sedation scores in the two groups. The Addenbrooke's sedation score used in this study may not have been sensitive enough to identify genuine differences and scores were obtained only every 4 h. The different analgesic regimens that were used after cardiopulmonary bypass may have influenced the postoperative patient sedation levels, but again we were unable to show any significant differences. It was technically impractical to blind the PCA systems but a strict extubation protocol was used to facilitate comparisons between the two groups.

There was no significant difference in the frequency and duration of episodes of myocardial ischaemia, cardiovascular instability and hypoxaemia in the two groups and no patient had postoperative myocardial infarction. The fact that only one patient in the study required sodium nitroprusside in the postoperative period is encouraging, and a reduced requirement for antihypertensive medication has been reported previously in patients receiving high-quality analgesia.[3 12] In the present study myocardial ischaemia was less frequent than in two uncontrolled previous studies, in which ischaemic events were reported in 48% and 40% of patients, respectively, after coronary artery bypass grafting.[13 14] The 19% frequency of ischaemia in our patients using the alfentanil patient-maintained analgesia system is similar to the 15% reported by Liem and colleagues in CABG patients who received high thoracic extradural analgesia.[3] However, it was significantly higher than the 4% frequency reported in another study that used prolonged high-dose opioid infusions in the postoperative period.[15]

Postoperative interviews with our patients before their discharge from hospital showed a high level of satisfaction with both patient-controlled analgesia systems. More patients in the alfentanil PMA group felt that their postoperative analgesia was excellent or good compared with those using the morphine PCA pump, but this difference was not significant. Patients had little difficulty in using the PCA handsets and this work has confirmed previous reports that PCA techniques can successfully be used by adult cardiac surgical patients in the immediate postoperative period.[16]

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Comparison of remifentanil in combination with isoflurane or propofol for short-stay surgical procedures†

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Summary

There are few data in the literature that describe the use of remifentanil when administered as a component of an inhalation or total i.v. anaesthetic (TIVA) technique. We studied 251 male and female patients, aged 18–75 years, ASA I–II, undergoing inguinal hernia repair, arthroscopic knee surgery or varicose vein surgery of at least 30 min duration without premedication. Patients were randomized to receive a remifentanil loading dose of 1.0 $\mu g\ kg^{-1}$ followed by a continuous infusion of 0.5 $\mu g\ kg^{-1}\ min^{-1}$ in combination with isoflurane (end-tidal concentration 0.6%), (Group I, $n = 115$) or propofol (initial infusion rate 9 mg $kg^{-1}\ h^{-1}$ reduced to 6 mg $kg^{-1}\ h^{-1}$ after 10 min), (Group P, $n = 118$). The remifentanil infusion rate was reduced by 50%, 5 min after tracheal intubation. Intraoperative stresses were treated with a remifentanil bolus (1 $\mu g\ kg^{-1}$) followed by an increase in the remifentanil infusion rate. At the insertion of the last suture, the remifentanil infusion and concomitant anaesthetic were switched off simultaneously. Times to spontaneous respiration, adequate respiration and tracheal extubation were significantly shorter in group I compared with group P (6.4 min *vs* 7.6 min, $P < 0.01$; 7.6 min *vs* 9.3 min, $P < 0.003$; 7.8 min *vs* 9.5 min, $P < 0.015$). Overall mean systolic blood pressures during surgery were greater in group P compared with group I ($P < 0.05$) but the absolute differences were clinically insignificant (4–5 mm Hg). (*Br. J. Anaesth.* 1998; **80**: 752–755)

Keywords: analgesics opioid remifentanil; anaesthetics volatile isoflurane; anaesthetic techniques total intravenous

Remifentanil is a 4-anilidopiperidine derivative and a specific μ-opioid receptor agonist with a potency similar to that of fentanyl[1] and a speed of onset similar to that of alfentanil.[2] However unlike any other available opioid remifentanil has an ester linkage in its molecular structure.[3] Consequently it has a very short duration of action because of rapid breakdown of the ester linkage by non-specific plasma and tissue esterases. The time for the plasma concentration to fall by 50% after stopping an i.v. infusion is short compared with that for other opioids; for example after a 3-h infusion of remifentanil or alfentanil the values were 3.1 and 44 min respectively.[4] Remifentanil is metabolized to a relatively inactive metabolite (potency 0. 1–0.3% compared with parent drug[5]).

These pharmacokinetic properties are consistent with a short predictable duration of action and no accumulation even after high doses or prolonged infusions. However there are few data in the literature describing the use of remifentanil when administered as a component of a inhalation or total intravenous anaesthetic (TIVA) technique. We therefore have studied the use of remifentanil under these circumstances.

Patients and methods

We performed a prospective, open, randomized, multicentre, parallel-group study in 26 hospitals in the United Kingdom. Patients (ASA I–II, 18–75 yr) undergoing inguinal hernia repair, arthroscopic knee surgery or varicose vein surgery of at least 30 min duration, and expected to stay in hospital overnight, were recruited after after we had obtained local ethics committee approval and written informed consent. Exclusion criteria were: hepatic or renal dysfunction, uncontrolled hypertension or a history of psychiatric disease; chronic use of opioids or benzodiazepines or administration of clonidine within 12 h of the study; known hypersensitivity to opiates, isoflurane or propofol; contraindications to the use of nonsteroidal anti-inflammatory drugs; in women, a positive pregnancy test on the day of surgery; body weight more than twice the ideal for the patient.

No premedication was given and patients were allocated randomly into one of two groups (TIVA or isoflurane) using a predetermined randomization code. Before induction of anaesthesia, all patients were preoxygenated for 3 min. Remifentanil 1 $\mu g\ kg^{-1}$ i.v. was given over 30–60 s followed by a continuous

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Table 1 Patient characteristics and duration and type of surgery (mean (SD) or number (%))

	Isoflurane (n=115)	TIVA (n=118)
Age (yr)	52 (15)	50 (14)
Weight (kg)	76 (13)	75 (16)
Sex		
Female	38 (33)	44 (37)
Male	77 (67)	74 (63)
Duration of surgery (min)	62 (25)	61 (24)
Type of surgery		
Arthroscopic knee	6 (5)	10 (8)
Hernia repair	58 (50)	46 (39)
Varicose vein	51 (44)	62 (53)

infusion of remifentanil 0.5 μg kg^{-1} min^{-1}. Anaesthesia was induced with propofol given at a rate of 1 mg sec^{-1} until loss of response to verbal command. Tracheal intubation was facilitated by vecuronium 0.1 mg kg^{-1} or atracurium 0.6 mg kg^{-1}.

The TIVA group then received a continuous infusion of propofol 9 mg kg^{-1} h^{-1}, reduced to 6 mg kg^{-1} after 10 min, and their lungs were ventilated with oxygen in room air to maintain oxygen saturation (Sp_{O_2}) above 94% throughout the procedure. The isoflurane group were given an oxygen/air mixture and isoflurane to maintain an end-tidal concentration of 0.6%. Five min after tracheal intubation, the remifentanil infusion was reduced to 0.25 μg kg^{-1} h^{-1} in both groups.

Arterial pressure (non-invasive) and heart rate were measured immediately before, and at 1 and 5 min after intubation, and then at 5-min intervals before skin incision. Arterial saturation and end-tidal carbon dioxide were maintained at 94–100% and 4.8–5.6 kPa respectively. Before skin incision, diclofenac 100 mg was given rectally for postoperative analgesia. After skin incision, blood pressure and heart rate were measured at 1 min and 5 min and at 5-min intervals thereafter until skin closure. If required, neuromuscular block was reversed with neostigmine (2.5–5.0 mg) and glycopyrrolate (0.5 mg) before the end of surgery. The decision whether to monitor neuromuscular block or to administer the reversal agents was made at the discretion of the investigator.

Intraoperative stresses — that is, somatic response; autonomic response; hypertension (defined as systolic blood pressure > 15 mm Hg above pre-operative baseline for at least 1 min) or tachycardia (heart rate > 90 beats min^{-1} for at least 1 min) — were treated with an incremental remifentanil dose (1.0 μg kg^{-1}), followed by an increase in the remifentanil infusion rate in steps of 0.125 μg kg $^{-1}$ min^{-1} as appropriate. Isoflurane or propofol administration was increased if no response occurred after four boluses and two remifentanil infusion rate increases within a 5-min period. Hypotension (defined as SBP < 80 mm Hg for at least 1 min) was initially treated with i.v. replacement therapy or, at the discretion of the investigator, controlled by an appropriate reduction in the propofol infusion or end-tidal isoflurane; bradycardia (heart rate < 40 beats min^{-1} for at least 1 min) or hypotension and bradycardia (heart rate < 50 beats min^{-1}) were treated with an anticholinergic agent.

At skin closure, and when considered appropriate by the investigator, the wound was infiltrated with 0.5% bupivacaine. At the end of surgery, propofol or isoflurane and remifentanil were stopped. The times to onset of spontaneous ventilation, adequate respiration (at least eight breaths min^{-1} or PE'_{CO_2} at < 50 mm Hg), tracheal extubation, and discharge from the recovery room were recorded. Aliquots of morphine 0.05 mg kg^{-1} i.v. were given for the control of postoperative pain at the discretion of the investigator from the onset of adequate ventilation, and in the recovery period.

On the day after surgery, patients were asked to complete a questionnaire about their experiences of postoperative nausea, emesis and wound pain. They were also asked if they remembered anything during surgery. Serious adverse events, both clinical and laboratory, were recorded.

Patient characteristics were compared using *t*-tests and chi-square tests. Recovery times were analysed by a conventional linear model,[6] averaging treatment effect across the participating centres. Systolic blood pressures were analysed by a linear "mixed" model.[7] The number of intraoperative interventions was analysed using a stratified permutation test,[8] the strata being the centres. In all statistical tests, the null hypothesis of "no population difference" was assumed and a two-sided *P*-value of ≤0.05 was considered statistically significant.

Results

A total of 251 patients were enrolled; 18 were withdrawn before receiving the first bolus dose of remifentanil, because: the operation was cancelled (nine patients); there were protocol violations (six); consent was withdrawn before induction (one); venous access was lost (one); or the investigator was called away from theatre (one). Of those who completed the study, 115 patients were in the isoflurane group and 118 in the TIVA group.

Table 2 Mean (SD) systolic blood pressure (mm Hg)

	Isoflurane			TIVA		
Time	Mean	SD	n	Mean	SD	n
Baseline	133	17	115	134	17	118
Loss of consciousness	122	23	113	125	23	116
1 min postintubation	104	22	111	107	19	115
5 min postintubation	95	19	112	100	16	118
1 min postincision	95	15	111	100	17	117
5 min postincision	97	14	110	101	17	114
10 min postincision	97	14	108	102	18	112
15 min postincision	97	14	106	101	16	107
20 min postincision	96	13	101	100	17	101
25 min postincision	97	14	93	100	16	94

Table 3 Mean (SD) recovery times

	Isoflurane			TIVA			
Indication of recovery	Mean	SD	*n*	Mean	SD	*n*	*P*
Spontaneous respiration	6.4	2.7	113	7.6	4.0	118	0.0098
Adequate respiration	7.6	2.9	113	9.3	4.6	118	0.0029
Extubation	7.8	2.8	113	9.5	4.1	118	0.0013
Qualification for recovery room discharge	41.6	27.1	112	45.3	25.4	118	0.38

There were no significant differences between the groups with respect to patient characteristics, duration or type of surgery (table 1).

Overall mean (SD) systolic blood pressures during surgery were greater in the propofol compared with the isoflurane group ($P < 0.05$), but the absolute differences were small (table 2). Intraoperative interventions to control hypertension were necessary in 10% of patients in the isoflurane group compared with 17% in the TIVA group ($P < 0.08$).

Mean (SD) times to spontaneous ventilation were 6.4 (2.7) min in the isoflurane group and 7.6 (4.0) min in the TIVA group, with rapid restoration of adequate respiration in both groups (table 3). All mean times were shorter in the isoflurane group but there was no difference in times to qualification for discharge from the recovery room.

Eighty-seven percent of patients completed their questionnaire within 24 h after surgery. Nausea was significantly less frequent in the TIVA group, but there was no difference in emesis. Most patients in both groups complained of no, mild or moderate pain. Only two (2%) in the TIVA group and six (6%) in the isoflurane group complained of severe pain (table 4). No patient recalled any events during surgery.

There were seven serious adverse events during the study: four wound haematomas, one urinary retention, two episodes of hypotension (one severe and one mild). Both episodes of hypotension resolved with fluids and anticholinergic agents. In one instance, the dose of remifentanil was adjusted, and in the other, the remifentanil dosage was left as per protocol. Both hypotensive episodes resolved with no further problems during surgery, and no adverse effect on outcome.

Table 4 Postoperative pain & PONV

	Isoflurane (n=115)		TIVA (n=118)
Nausea			
None	54 (50%)		77 (68%)
Mild	35 (33%)		26 (23%)
Moderate	12 (11%)		7 (6%)
Severe	7 (6%)		3 (3%)
		p=0.006	
Emesis			
No emesis	90 (86%)		98 (89%)
Emesis	15 (14%)		12 (11%)
		p=0.54	
Wound pain			
None	24 (22%)		30 (26%)
Mild	49 (45%)		57 (50%)
Moderate	30 (28%)		25 (22%)
Severe	6 (6%)		2 (2%)
		p=0.094	

Discussion

We have shown that, after isoflurane anaesthesia or TIVA of a mean duration of approximately 60 min, there is a rapid onset of spontaneous ventilation and then adequate ventilation after cessation of a remifentanil infusion. Recovery was more rapid in the isoflurane group, although clinically the difference was insignificant. Systolic blood pressure was generally greater in the TIVA group during the procedure but this difference was not significant clinically. Nausea was more frequent in the isoflurane group but there was no difference in the incidence of emesis.

This report is one of the first describing general anaesthetic techniques using recommended doses of remifentanil. The main purpose was to measure times to recovery in a large group of patients. We have also made comparisons between the two groups and found significant differences. Clearly, this was an open study and none of the observations were made in a blind manner: the conclusions based on the comparisons of the two groups are therefore relatively weak. The usual problems with multicentre studies apply here but the anaesthetic protocol was controlled strictly and we believe that the recovery data are valid. Mean time to spontaneous ventilation was 6.4 min in the isoflurane group and 7.6 min in the TIVA group. Recovery times in this study are similar to those found by Schüttler and colleagues,[9] who reported a mean time to spontaneous ventilation of 7 min and a mean time to adequate respiration of 10 min. However, their mean time to extubation of 12 min is greater than that seen in either group in the present study (7.8 min inhaled, 9.5 min TIVA). It is likely that the recovery times were slower than in our study as patients were premedicated with oral midazolam (7.5 mg) or diazepam (5–10 mg).

Times to extubation in the present study were similar to those presented in an abstract by Monk and colleagues,[10] who reported a mean extubation time of 8.5 min after an infusion of remifentanil 0.25 $\mu g\ kg^{-1}\ min^{-1}$ The corresponding time for alfentanil in that study was 17 min.

Episodes of hypertension or tachycardia occurred in 10% of patients in the isoflurane group and 17% in the TIVA group. Most of these responded to administration of further remifentanil, which was a therapeutic option even towards the end of the procedure because of the agent's short half-life. An inherent problem with studies of this nature is that the investigators are obliged to react to events according to a strict protocol. It is likely that these episodes would be less frequent if the anaesthetist was able to respond to events in a more rapid and pre-emptive fashion as occurs in normal clinical practice.

Adequacy of reversal of neuromuscular block was assessed by the investigating anaesthetist and whether to use a neuromuscular monitor was his or her decision. We accept this is an uncontrolled variable but in a study of this size we believe it is not likely to affect the results significantly.

Although the primary purpose of this study was not to investigate postoperative pain, and the administration of postoperative analgesia was not controlled strictly, the patient questionnaire indicates that pain control was satisfactory in most patients. However, this was relatively minor surgery, diclofenac suppositories were administered, and infiltration of the wound with local anaesthetic or morphine or both were used when appropriate. After more extensive surgery, it is likely that pre-emptive opioids will be required before the end of the procedure; this is being investigated.

In conclusion, we have shown rapid recovery of spontaneous ventilation when remifentanil was used as the analgesic component of an isoflurane or propofol infusion anaesthetic technique. The use of remifentanil in general anaesthesia warrants further study.

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Effect of pre-treatment with intravenous atropine or glycopyrrolate on cardiac arrhythmias during halothane anaesthesia for adenoidectomy in children

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Summary

We studied the effect of anticholinergics on the incidence of cardiac arrhythmias during paediatric anaesthesia. ASA I-II children (*n*=77) undergoing adenoidectomy were randomly allocated to three groups. Intravenous atropine 0.02 mg kg^{-1} was given in group A (*n*=25), glycopyrrolate 0.004 mg kg^{-1} in group G (*n*=27) and physiological saline in group P (*n*=25) 3 min before the induction of anaesthesia. The children breathed spontaneously under halothane anaesthesia with 66% nitrous oxide in oxygen after induction with thiopentone and succinylcholine. Perioperative monitoring of the ECG (Holter recordings) and oxygen saturation was carried out. Ventricular tachycardia occurred in 16.0%, 18.5% and 12.0% of the children in groups A, G and P respectively (ns). The incidence of ventricular arrhythmias (ventricular tachycardia, ventricular bigeminy, ventricular premature beats >10) was 20.0% in group A, 44.4% in group G and 36.0% in group P (ns). Bradycardia (<70 beats min^{-1}) was observed in 0.0%, 14.8% and 24.0% of patients in groups A, G and P respectively (A *vs* P, $P<0.05$). The use of anticholinergics did not influence the incidence of ventricular arrhythmias during halothane anaesthesia in children. Bradycardia was more common in the placebo group than in the atropine group. (*Br. J. Anaesth.* 1998; **80**: 756–760)

Keywords: anaesthesia paediatric; anaesthetics volatile halothane; arrhythmias cardiac; premedication atropine glycopyrrolate

In paediatric anaesthesia, the use of halothane and succinylcholine can cause bradycardia.[1 2] Anticholinergics are given to such patients to prevent vagal reflexes and salivation.[3 4] In addition, atropine attenuates the halothane-associated reduction of cardiac output in children.[5] However, the routine use of anticholinergic agents in paediatric anaesthesia remains controversial. In some studies, atropine and glycopyrrolate produced ventricular arrhythmias in children and adults.[6–8] Badgwell and colleagues demonstrated that junctional rhythms occurring in children over 1 yr old anaesthetized with halothane usually resolve spontaneously.[9] They suggested that anticholinergics are not required in these children for the purpose of preventing junctional arrhythmias. In adults, the use of anticholinergics as premedicants is declining.[10] Experimental studies have shown that vagal activation protects the heart against ventricular fibrillation and atropine or vagotomy abolishes this protective effect.[11 12]

The incidence of cardiac arrhythmias is high during oral surgery.[13 14] However, the arrhythmogenic or antiarrhythmogenic properties of atropine or glycopyrrolate have not been compared in a placebo-controlled study in children anaesthetized with halothane for adenoidectomy. Because of the controversy in the literature, the aim of our study was to clarify the role of anticholinergics in paediatric anaesthesia with particular regard to the incidence of cardiac arrhythmias. To ensure complete data collection, Holter monitoring of the ECG was performed. In this double-blind, randomized study, we chose a dose of atropine that would have a definite cardiac effect, and compared it with a small dose of glycopyrrolate to find out the minimum effective dose of glycopyrrolate to prevent bradycardia.

Patients and methods

The study was approved by the Ethics Committee of Tampere University Hospital and written informed consent was obtained from the parents of each child investigated. Seventy-seven ASA I-II children undergoing adenoidectomy were randomly assigned into three groups, using a list of numbers 1 to 90 randomized to the three groups. Patients were listed in order of recruitment. Atropine (0.02 mg kg^{-1}) was given intravenously in group A (*n*=25), glycopyrrolate (0.004 mg kg^{-1}) in group G (*n*=27) and physiological saline (same volume, 0.02 ml kg^{-1}) in group P (*n*=25). Syringes were prepared and labelled with the patients' identification numbers by nurses not involved in the study. Only children weighing 10–20 kg were included. Patient characteristics are shown in table 1. The children were premedicated with rectal diazepam 0.5 mg kg^{-1} and paracetamol 10 mg kg^{-1}, 30 min before anaesthesia. EMLA (Astra, Sweden) cream was applied to the dorsum of the

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Table 1 Patient characteristics (mean (SD)). No significant differences between groups

	Group A (n=25)	Group G (n=27)	Group P (n=25)
Age (months)	30.4 (14 4)	38.4 (18.7)	37.4 (22.0)
Weight (kg)	13.1 (2.8)	14.6 (3.6)	14.0 (3.6)
Height (cm)	90.8 (9.8)	95.1 (3.1)	94.0 (13.1)

hand 1 h before venous cannulation. If the vein was punctured more than once, the child was excluded from the study.

Fifteen minutes before the induction of anaesthesia, a Holter ECG recording (Oxford Medilog tape recorder, leads V1 and V5) was started, and continued until the children were fully awake in the recovery room. The study was performed in a double-blind manner: neither the anaesthetist nor the analyst of the recordings (PR), which were analysed with a Daltek system at the department of clinical physiology, knew to which group the child was assigned. Arterial pressures were measured non-invasively by cuff manometry before administration of the study drug, immediately after tracheal intubation and extubation, 2 and 5 min after intubation and at 5-min intervals thereafter until the end of the study. Heart rate was calculated as a mean of four consecutive complexes from Holter recordings. ECG (lead II) was continuously monitored. Ventricular tachycardia was defined as three or more consecutive complexes of VBPs. When ventricular premature beats (VPBs) occurred three times in turn with a normal QRS complex, arrhythmia was defined as ventricular bigemini. Also, if the number of VPBs or supraventricular extrasystoles (SVEs) exceeded 10 in a period of 5 min, it was regarded as an arrhythmic event.

The study drug was given i.v. 3 min before thiopentone 5 mg kg^{-1}. The trachea was intubated after succinylcholine 1 mg kg^{-1}, and anaesthesia was continued with nitrous oxide 66% in oxygen and halothane. The children breathed halothane (1.5–2.5 vol %) spontaneously via a Bain system. The total gas flow was 6 l min^{-1} to prevent rebreathing.[15] The children were manually ventilated if oxygen saturation (Sp_{O_2}), measured by pulse oximetry (Ohmeda Biox 3700e), decreased below 92% and the event was noted. For study purposes, adenoidectomy started 5 min after intubation. The children were extubated during spontaneous breathing of halothane after 2 min of oxygenation with 100% oxygen. End-tidal carbon dioxide (PE'_{CO_2}) was continuously monitored during anaesthesia (Datex Normocap) via a sampling catheter mounted in the tracheal tube. If heart rate decreased below 60 beats min^{-1} (bpm) for 5 s, atropine 0.02 mg kg^{-1} was available as a rescue drug in a syringe, and the necessary dose for each patient was calculated before induction. In this study, we registered bradycardias below 70 beats min^{-1}. The normal range for heart rate at 2 years of age is 105±25 beats min^{-1}.[16]

In the recovery room, all the children were observed by the same nurse. Estimation of salivation was on an open scale scoring from 1 (no salivation) to 9 (excessive salivation), recorded at 5, 10, 20, 40 and 60 min after the end of surgery. In addition, any complications during the 60-min period were noted.

STATISTICAL ANALYSIS

Analyses were performed with a BMDP statistical software package. Statistical comparison between the groups was performed using a two-way analysis of variance (ANOVA) with Bonferroni's correction and a paired t test. The chi-square test was used to test the significance of the frequency of cardiac arrhythmias between the groups. Non-parametric data were analysed by Kruskal–Wallis and Mann–Whitney tests. Data are reported as mean (SD). $P<0.05$ was considered statistically significant.

Results

The distribution of weight, height and ages of children was similar in all three groups (table 1). Ninety children were recruited but, because of technical difficulties, only 77 Holter recordings were faultless and acceptable for the study. There were no between-group differences in the baseline values of heart rate or systolic arterial pressure (SAP). After tracheal intubation, heart rate had increased in all groups. In patients receiving atropine, heart rate increased significantly more than in the other patients ($P<0.001$ between group A and group G and between group A and group P). Furthermore, heart rate remained elevated throughout the study at every time point after atropine, but decreased after intubation in the other groups (fig. 1).

Bradycardia (<70 beats min^{-1}) was observed in none, four (14.8%) or six (24.0%) patients in groups A, G and P respectively ($P<0.05$ between A and P) (table 2). In patients receiving glycopyrrolate, all bradycardic events occurred during anaesthetic induction or tracheal intubation. In patients receiving saline, bradycardia occurred during surgery except for one patient, who also had a bradycardic event during induction of anaesthesia. All bradycardic episodes were short — of less than 5 s duration — so no medication was needed. The events were not

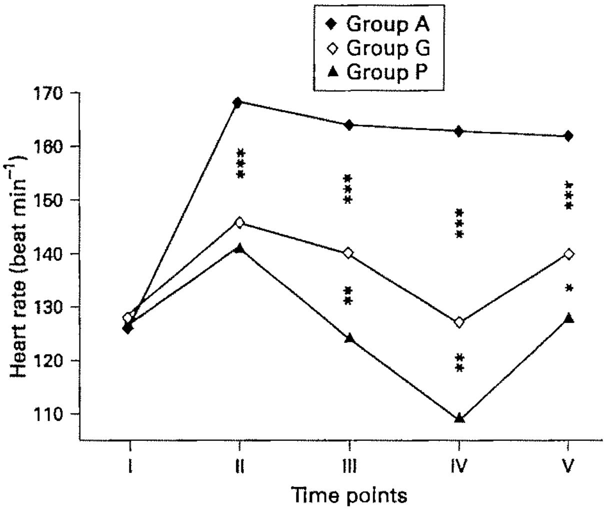

Figure 1 Mean heart rates during the study in groups of children who received pretreatment before halothane anaesthesia with intravenous atropine (Group A), glycopyrrolate (Group G) or placebo (Group P). Timepoints: I=before the study drug; II=after intubation; III=2 min after intubation; IV=5 min after intubation; V=after extubation. ***$P<0.001$ between group A and group P and between group A and group G. **$P<0.01$ between group G and group P. *$P<0.05$ between group G and group P.

Table 2 Classification of cardiac arrhythmias after administration of the study drug. Ventricular tachycardia (VT), ventricular bigemini (VB), ventricular premature beats (VPB), supraventricular extra systoles (SVEs). $^{*}P<0.05$ compared with group A. $^{***}P<0.001$ compared with groups G and P

	Group A (n=25)	Group G (n=27)	Group P (n=25)
Ventricular arrhythmias			
VT	4	5	3
VPB (>10) or VB	1	7	6
Supraventricular arrhythmias			
Bradycardia (<70 beat min^{-1})	—	4	6*
SVEs (>10)	—	1	2
Sinus tachycardia (>170 beat min^{-1})	23***	12	9

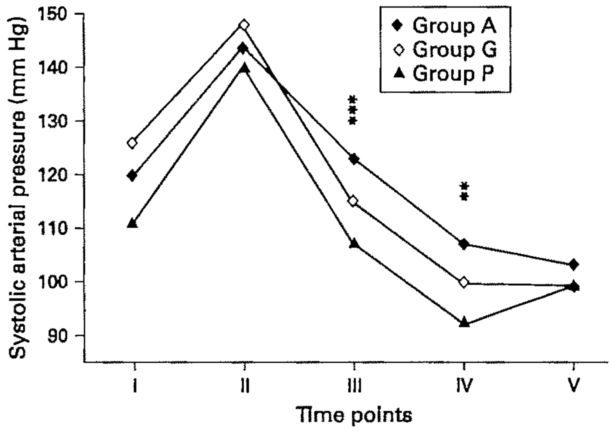

Figure 2 Mean systolic arterial pressures during the study. Groups and time points as in fig. 1. $^{***}P<0.001$ and $^{**}P<0.01$ between group A and group P.

associated with a low Sp_{O_2}. Tachycardia (>170 beats min^{-1}) was more common in the atropine group than in the saline or glycopyrrolate groups (table 2).

Systolic arterial blood pressures changed in a similar way in all patients, although the pressures were higher in group A than in group P (fig. 2). Arterial pressures increased after intubation and decreased afterwards (fig. 2).

Ventricular tachycardia, that is, three or more consecutive ventricular complexes, was seen in four, five and three patients in groups A, G and P respectively (ns) (table 2). The total number of ventricular arrhythmic episodes (more than 10 ventricular premature beats in 5 min, ventricular bigeminia or ventricular tachycardia) was five in group A, 12 in group G and 9 in group P (ns). These episodes occurred mainly during surgery or during tracheal extubation after surgery. Only one child in group A (ventricular tachycardia), one in group G (VPBs) and one in group P (ventricular bigemini) had arrhythmias during anaesthetic induction or tracheal intubation. One child in group G and two children in group P had more than 10 supraventricular extrasystolic beats (SVEs) in 5 min (table 2); the patient in group G already had SVEs before receiving the study drug. Ventricular premature beats were seen in one patient (group G) before glycopyrrolate; this child also had ventricular bigemini during tracheal intubation. All episodes of ventricular arrhythmia were short and no treatment was needed. Examples of arrhythmias described are shown in fig. 3.

The $P\text{E}'_{O_2}$ values ranged between 6.5 and 8.5 kPa during the study. During recovery from anaesthesia,

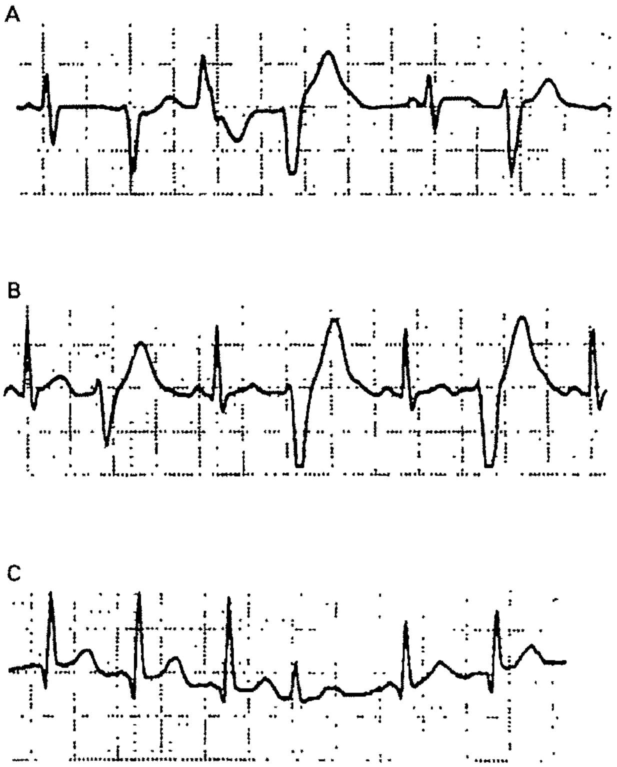

Figure 3 Examples of arrhythmias. A=ventricular tachycardia; B=ventricular bigemini; C=supraventricular extrasystoles (SVEs).

salivation was more severe in the patients who had received saline ($P<0.001$) than in those receiving atropine or glycopyrrolate; no difference was seen between group A and group G. Minor complications were seen in three of the 77 patients: one child in the atropine group and one in the glycopyrrolate group had laryngospasm. One child in the atropine group had laryngitis after operation.

Discussion

Our results show that there is no difference in the incidence of ventricular arrhythmias during adenoidectomy in children pretreated with atropine, glycopyrrolate or saline. The accuracy of the data were verified by perioperative Holter recording of the ECG. To our knowledge, the present study is the first to compare the effect of glycopyrrolate with that of atropine and saline.

Warran and co-workers found that the incidence of ventricular arrhythmias after i.v. atropine and i.v. glycopyrrolate is identical.[17] Our results were similar to that study. Sigurdsson and colleagues reported that in children, the incidence of ventricular arrhythmias is increased after diazepam–atropine premedication, compared with that after diazepam–morphine–hyoscine.[18] Johannesson and colleagues showed similar results with diazepam–atropine *vs* diazepam–morphine–scopolamine during adenoidectomy in children.[19] As Sigurdsson and co-workers concluded,[18] more effective sedative premedication reduces the sympathetic and endocrine response to surgery, altering the incidence of arrhythmias. This was probably the case in both of those studies.[18 19] Anticholinergic agents alter the balance between sympathetic and parasympathetic activity in the autonomic nervous system by blocking the parasympathetic muscarinic receptors.[11] In adults, sympathetic predominance may cause arrhythmias.[8 20] Furthermore, cardiac vagal activity is an important protector against sudden cardiac death.[21] Our results do not support the suggestion that anticholinergics are arrhythmogenic. The autonomic nervous system of children may react differently compared with that of adults.

Bradycardia (<70 beats min^{-1}) was more common in children receiving saline than in those to whom atropine was given. However, in all the children, even those in the saline group, the events were short and resolved spontaneously. Persisting sinus tachycardia (>170 beats min^{-1}), occurred in 23 of the 25 patients in the atropine group. This hyperdynamic state, together with the well known effects of atropine on the central nervous system, may contribute to the discomfort (flushing, irritability) that children experience in the recovery room.[22] Our results strongly suggest that atropine, rather than being used routinely, could well be kept as a drug only for unresolved bradycardias during adenoidectomy.

The effect of glycopyrrolate in preventing bradyarrhythmias is dose related.[23] We used a relatively small dose of glycopyrrolate (0.004 mg kg^{-1}) to study its effectiveness in preventing bradycardia. The effect of glycopyrrolate on haemodynamic variables was moderate compared with that of atropine. However, the doses used in this study (glycopyrrolate 0.004 mg kg^{-1} *vs* atropine 0.02 mg kg^{-1}) were not equipotent; Lerman and Chinyanga concluded that atropine 0.02 mg kg^{-1} is equipotent with glycopyrrolate 0.01 mg kg^{-1}.[23]

Probably in part because of the small dose of glycopyrrolate used in the present study, bradycardic events were seen four times in group G compared with six times in group P. Bradycardias tended to occur during induction in patients receiving glycopyrrolate but during surgery in patients receiving saline. The effect of glycopyrrolate, however, starts within 2 min[24] and reaches its maximum by 3–7 min.[25] Therefore, it is possible that the 3-min waiting time before anaesthetic induction was too short to prevent bradycardic episodes in some of our patients. Lavis and colleagues have shown that heart rate does not change as rapidly after i.v. glycopyrrolate (0.005 mg kg^{-1}) as it does after i.v. atropine (0.01 mg kg^{-1}).[4] Thereafter heart rate remained at the same level after both drugs.[4] In our patients, the antisialogue effect of glycopyrrolate was obvious, proving the anticholinergic properties of this drug.

We used a relatively high dose of atropine to study the arrhythmogenic properties, if any, of atropine in this analysis, which was verified by Holter recording of the ECG. Palmisano and colleagues recommended at least atropine 0.01 mg kg^{-1} with halothane and nitrous oxide in children.[26] The dose of atropine 0.01 mg kg^{-1} is suggested to be as effective as 0.02 mg kg^{-1} in preventing bradycardia, with fewer side effects.[27] Our placebo-controlled study suggests that a high dose of atropine does not cause ventricular arrhythmias during halothane anaesthesia and that a small dose of glycopyrrolate, given early enough, is probably as effective in preventing bradycardia.

During spontaneous breathing under halothane, $P\mathrm{E}'_{\mathrm{O}_2}$ tensions are higher than in controlled ventilation, sometimes exceeding the physiological limit. Hypercarbia is known to produce arrhythmias.[28] During halothane–nitrous oxide anaesthesia the median arrhythmic threshold is greater than 10.7 kPa.[28] This was not reached in our patients. Therefore, raised $P\mathrm{E}'_{\mathrm{O}_2}$ does not explain the incidence of arrhythmias in this study. Hypoxia was prevented by manual ventilation, if necessary, and therefore arrhythmic episodes should not stem from a hypoxic origin.

The incidence of ventricular arrhythmias is related to the inhalation agent used.[29] With halothane, the incidence of arrhythmias is higher than with enflurane or isoflurane.[19] It has also been shown by Sigurdsson and colleagues that arrhythmias were significantly fewer in children who received halothane anaesthesia for myringotomies compared with adenoidectomy.[29] In their study, there were almost no dysrhythmias in children receiving enflurane.

In conclusion, the incidence of ventricular arrhythmias during halothane anaesthesia in children was similar after pretreatment with atropine, glycopyrrolate or saline. Atropine prevented bradycardic events but caused persisting sinus tachycardia in most patients. Bradycardic events were short and recovered spontaneously in patients receiving glycopyrrolate or saline. This study suggests that routine pretreatment with anticholinergic agents is unnecessary in children undergoing adenoidectomy during halothane anaesthesia.

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Tropisetron reduces vomiting after tonsillectomy in children

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Summary

Nausea and vomiting are common after adenotonsillectomy. Tropisetron is a new, long-acting serotonin antagonist that is an effective antiemetic in adults. Its effect on postoperative nausea and vomiting in children is unknown. We carried out a randomized, double-blind study of the effects of a single i.v. dose of tropisetron on vomiting after tonsillectomy with or without adenoidectomy in children. Forty-eight children undergoing tonsillectomy or adenotonsillectomy received at induction of anaesthesia either tropisetron 0.1 mg kg^{-1} or placebo. The incidence of vomiting was recorded for the first 24 h after surgery by nursing staff and then by parents after discharge from hospital. Children received metoclopramide 0.15 mg kg^{-1} as a rescue antiemetic. We found that tropisetron reduced the overall incidence of emetic episodes after surgery (29% compared with 65% in control group; $P = 0.019$) and the incidence of severe vomiting (0% compared with 52% in control group; $P < 0.001$). We conclude that tropisetron is an effective antiemetic for children undergoing tonsillectomy. (*Br. J. Anaesth.* 1998; **80**: 761–763)

Keywords: children; surgery tonsillectomy; vomiting, antiemetics tropisetron

The incidence of vomiting after adenotonsillectomy in children is as high as 73%.[1] Vomiting in this group of children causes unnecessary discomfort and distress and is one of the factors limiting day-case tonsillectomy. Different anaesthetic techniques and antiemetic drugs have been used to reduce the incidence of vomiting after tonsillectomy, with variable success.[2 3] Ondansetron reduces the incidence and severity of post-tonsillectomy vomiting in children,[1] but its effect may decrease beyond 4 h after surgery.[4]

Tropisetron is a new $5HT_3$ antagonist that has a long elimination half-life and need be given only once daily.[5] It is a safe and effective antiemetic in children receiving chemotherapy[6] and has also been shown to prevent post-operative vomiting in adults,[7 8] although with variable efficacy.[9] The effect of tropisetron on postoperative nausea in children has not been studied.

We conducted a randomized, double-blind, placebo-controlled study to evaluate the efficacy of tropisetron used as a single i.v. dose for the prevention of vomiting in children within the first 24 h after tonsillectomy or adenotonsillectomy.

Patients and methods

After obtaining approval from the hospital ethics committee and written informed parental consent, we studied 48 children (aged 2–12 yr, ASA I or II) scheduled to undergo elective tonsillectomy or adenotonsillectomy. Children who had cardiac, renal or liver disease were excluded.

Children were premedicated with oral paracetamol 15 mg kg^{-1} and EMLA cream applied to both hands 1 h before surgery. Anaesthesia was induced with thiopentone 4–5 mg kg^{-1} or halothane, followed by atracurium 0.5 mg kg^{-1}. Immediately after tracheal intubation, children received i.v. tropisetron 0.1 mg kg^{-1} or normal saline. We used a random number table with blocked randomization to allocate children to treatment groups. The volume of study drug was standardized to 0. 1 ml and was drawn up by a staff member who took no further part in the study.

Anaesthesia was maintained using positive pressure ventilation, nitrous oxide and oxygen mixture and isoflurane or halothane, with i.v. pethidine 1 mg kg^{-1} for analgesia. At the end of the surgical procedure, residual neuromuscular block was antagonized with atropine 0.02 mg kg^{-1} and neostigmine 0.05 mg kg^{-1}. During recovery, i.v. pethidine 0.25 mg kg^{-1} at 3-min intervals was given as required to control pain. On the ward, analgesia was provided by i.m. pethidine 1–1.5 mg kg^{-1} every 4 h, or oral paracetamol with or without codeine.

Observations were made by nursing staff who were blinded to the antiemetic used. Retching and vomiting were grouped under the common term "emetic episode". Vomiting was defined as the forceful expulsion of a measurable amount of gastric contents. When no stomach contents were expelled, the expulsive efforts were classified as retching. The incidence of emesis was evaluated at five intervals over the first 24 h following operation: 0–2 h, 2–6 h, 6–12 h, 12–18 h, and 18–24 h.

Any child who had three or more emetic episodes received metoclopramide 0.15 mg kg^{-1} as rescue medication. Children were offered oral fluids when they were alert enough to tolerate them. In children discharged from hospital before 24 h, the incidence of emetic episodes was ascertained by telephone follow-up.

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Table 1 Patient characteristics (mean (SD)) or number

	Control (n=23)	Tropisetron (n=24)
Age (yr)	6.3 (2.6)	5.7 (2.5)
Sex (M/F)	12/11	14/10
Weight (kg)	26.0 (12.4)	23.2 (10.1)
Tonsillectomy	4	4
Adenotonsillectomy	19	20
Duration of surgery (min)	25 (10)	25 (12)
Average hospital stay (h)	20.5 (2.9)	20.5 (3.1)
Average dose of pethidine (mg kg^{-1})	1.2 (0.3)	1.2 (0.5)

Sample size was calculated on the basis of desire to detect a reduction in the incidence of vomiting from 75% in the placebo group to 30% in the tropisetron group, with a type I error rate of 0.05 and a power of 0.8. Parametric data were compared using Student's t test. The incidence of vomiting during each interval and use of rescue antiemetic were compared using the Fisher exact test. $P < 0.05$ was taken as significant.

Results

We studied 48 children but data for one child in the control group were excluded because of protocol violation (metoclopramide was given during operation). The two groups were comparable for age, sex, weight and duration and type of surgical procedure (table 1). Anaesthesia was induced intravenously in most children; gas was used in only four children in the control group and two in the tropisetron group. The total dose of pethidine ranged from 0.8 mg kg^{-1} to 2 mg kg^{-1}, the range of doses being similar in both groups. In the control group, only one child had 2 mg kg^{-1} of pethidine and vomiting was observed. Four children in the tropisetron group received 2 mg kg^{-1} and of these, two vomited while two did not. Ten children in each group were given i.m. pethidine after surgery.

We found that tropisetron reduced the incidence of vomiting. Fifteen children in the control group (65%) had one or more emetic episode compared with seven (29%) in the tropisetron group (P = 0.019) (fig. 1). We also found that vomiting was more severe in the control group. Of the children who vomited, 12 (52%) in the control group had three or more emetic episodes compared with none in the tropisetron group ($P < 0.001$). Only five of the children in the control group who had three or more emetic episodes received metoclopramide as rescue medication. In the control group, most children had emetic episodes in the first 12 h after operation. In the tropisetron group, the incidence of vomiting followed no discernible time pattern (fig. 1). The average length of stay in hospital was 20.5 h in both groups. Nineteen children in the tropisetron group and 20 children in the control group were discharged home less than 24h after surgery, and were followed up by telephone. Three children could not be contacted by telephone after discharge. The rest of the children in both groups had no vomiting after discharge.

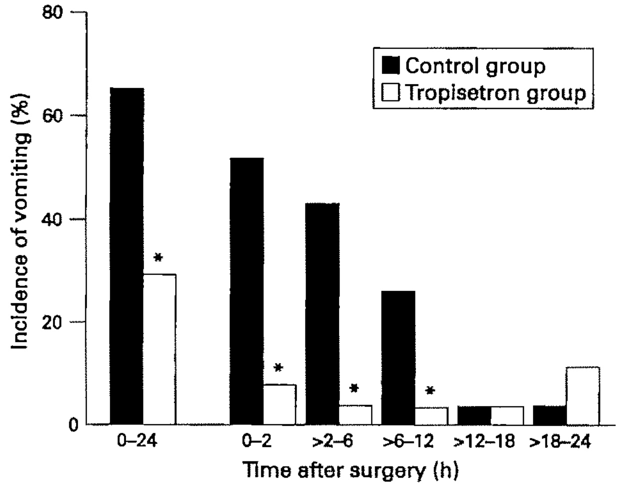

Figure 1 Incidence of vomiting after tonsillectomy or adenotonsillectomy in children who received either i.v. tropisetron 0.1 mg kg^{-1} (n = 24) or placebo (n = 23). *$P < 0.05$.

Discussion

We found that tropisetron was an effective antiemetic for children undergoing tonsillectomy. The incidence of vomiting was 65% in the control group but only 29% in children who had received tropisetron. Tropisetron also reduced the severity of vomiting, with 12 (52%) in the control group vomiting more than three times compared with none in the tropisetron group.

Tropisetron is a highly selective, competitive antagonist of the $5HT_3$ receptor. $5HT_3$ receptor antagonists lack the dysphoric and extrapyramidal effects of metoclopramide and droperidol.[10 11]

The antiemetic effects of tropisetron have been studied in children receiving chemotherapy; in this group, tropisetron has a plasma terminal half-life of 5.3–6.6 h.[6] Ondansetron was found to have a plasma terminal half-life of 2.6–3.1 h in children undergoing surgery.[12] Ondansetron was effective in preventing vomiting for only the first 4 h after surgery in one study,[4] and in another, two doses of ondansetron were more effective than one dose in children undergoing tonsillectomy.[13] The longer plasma elimination half-life of tropisetron may be advantageous in children at risk of postoperative nausea and vomiting. We saw no increase in the incidence of vomiting in our children during the 24 h after surgery. Furthermore, no child in the tropisetron group received rescue therapy, which might otherwise have masked a rise in the incidence of postoperative vomiting.

The dose of tropisetron used in our study was 0.1 mg kg^{-1}, which is similar to the dose used in adult studies of postoperative nausea and vomiting, but smaller than that used in paediatric chemotherapy studies.

Swallowed blood contributes to the high incidence of vomiting after tonsillectomy. There has been concern that use of an antiemetic after tonsillectomy might allow swallowed blood to accumulate in the stomach and conceal postoperative haemorrhage. Although there have been anecdotal reports of this occurring, just how effective antiemetics are at preventing vomiting when there is a large amount of blood in the stomach is unknown. Postoperative haemorrhage occurs in less than 1% of cases and retching and vomiting may even contribute by causing venous engorgement. The key to picking up early signs of haemorrhage is conscientious postoperative observation of vital signs and not only the observation of actual blood loss. If antiemetics are deliberately withheld to avoid concealing postoperative haemorrhage, many children will be left to vomit and suffer after tonsillectomy.

In addition to swallowed blood, opioid drugs given for postoperative analgesia may induce vomiting. All children received pethidine during surgery, and all but one child received a dose of 1 mg kg^{-1}. However, the amount of pethidine given postoperatively could not be standardized as this was determined by the analgesic requirements of the child. Nevertheless, both groups received a similar total dose of pethidine.

We had hoped that the administration of metoclopramide would be a reflection of the severity of vomiting, as the study protocol called for its administration in children who had vomited three or more times. However, we found that of the 12 children who had vomited three or more times, only five received metoclopramide. We believe that nursing staff were reluctant to use metoclopramide because of fear of possible side effects.

Vomiting is a distressing yet common postoperative complication. In children undergoing tonsillectomy, vomiting as well as postoperative pain can be particularly stressful for both child and parent. Tropisetron, by decreasing the incidence and severity of vomiting, contributes to a less stormy postoperative course.

Acknowledgement

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Granisetron in the prevention of nausea and vomiting after middle-ear surgery: a dose-ranging study

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Summary

This study was undertaken to determine the minimum effective dose of granisetron, a selective 5-hydroxytryptamine type 3 receptor antagonist, for the prevention of postoperative nausea and vomiting (PONV) after middle-ear surgery. In a randomized, double-blind, placebo-controlled trial, 120 women (ASA I) received placebo (saline) or granisetron at three different doses (20 μg kg^{-1}, 40 μg kg^{-1}, 100 μg kg^{-1}) i.v. immediately before the induction of anaesthesia (*n*=30 for each group). A standard general anaesthetic technique was used throughout. A complete response, defined as no PONV and no need for another rescue antiemetic during 0–3 h after anaesthesia, occurred in 40%, 43%, 83% and 87% of patients who had received placebo, granisetron 20 μg kg^{-1}, granisetron 40 μg kg^{-1} or granisetron 100 μg kg^{-1}, respectively; the corresponding incidence during 3–21 h after anaesthesia was 47%, 47%, 87% and 87% ($P<0.05$; overall Fisher's exact probability test). Granisetron 40 μg kg^{-1} appears to be the minimum effective dose for preventing PONV in women undergoing middle-ear surgery. (*Br. J. Anaesth.* 1998; **80**: 764–766)

Keywords: pharmacology granisetron; vomiting nausea antiemetics; surgery ear

The incidence of nausea and vomiting after middle-ear surgery varies from 62% to 80% with no antiemetic treatment.[1–3] Granisetron, like ondansetron, is a selective antagonist of the 5 hydroxytryptamine type 3 (5-HT$_3$) receptor, and is effective for the treatment of emesis in patients receiving cytotoxic drugs.[4] Granisetron has a more potent and longer activity than ondansetron against emesis associated with chemotherapy.[5] We have recently shown that it reduces the incidence of nausea and vomiting after middle-ear surgery.[6] The present study was undertaken to determine the minimum effective dose of granisetron for the prevention of postoperative nausea and vomiting (PONV), in a randomized, double-blind comparison with placebo, in women undergoing middle-ear surgery.

Patients and methods

After obtaining institutional review board approval and informed consent, we studied 120 female patients (ASA I, aged 25–60 yr) undergoing middle-ear surgery (tympanoplasty or mastoidectomy). Patients with gastrointestinal disease, those with a history of motion sickness or previous PONV or both, those who were pregnant or menstruating, or who had taken antiemetics within 24 h before surgery were excluded from the study.

Patients received no preanaesthetic medication and, in a randomised, double-blind manner, a single dose of placebo (saline) or granisetron at three different doses (20 μg kg^{-1}, 40 μg kg^{-1}, 100 μg kg^{-1}) i.v. over 2–5 min immediately before the induction of anaesthesia. Anaesthesia was induced with thiopentone 5 mg kg^{-1} i.v., and vecuronium 0.2 mg kg^{-1} i.v. was used to facilitate tracheal intubation. After tracheal intubation, anaesthesia was maintained with 1.0–3.0% (inspired concentration) isoflurane and nitrous oxide 66% (which was replaced by air before closing of the tympanic membrane) in oxygen. No patient received opioids before tracheal intubation or during the maintenance of anaesthesia. Ventilation was mechanically controlled and was adjusted to maintain an end-tidal concentration of carbon dioxide between 4.6 kPa and 5.2 kPa throughout surgery with an anaesthetic/respiratory analyser (Ultima, Datex, Helsinki, Finland). Muscle relaxation was achieved with vecuronium and antagonized by a combination of atropine 0.02 mg kg^{-1} i.v. and neostigmine 0.04 mg kg^{-1} i.v. at the end of surgery. The trachea was extubated when the patient was awake. Placement of a nasal or oral gastric tube during surgery was not permitted. Rectal temperature was monitored and maintained at 37±1°C throughout surgery. If two or more episodes of vomiting occurred during the first 24 h after anaesthesia, a rescue antiemetic (for example, metoclopramide 0.2 mg kg^{-1}) was given. After operation, patients received indomethacin 50 mg as required when they complained of pain. After operation, all episodes of PONV (nausea, retching, vomiting) during the first 24 h after anaesthesia (that is, 0–3 h in the post-anaesthetic unit and 3–24 h in the ward) were recorded by nursing staff unaware of which treatment patients had received. A complete response was defined as no PONV and no need for a rescue

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Table 1 Patient characteristics and surgical details. Values are mean (SD or range) or number. No significant differences

	Placebo (n=30)	Granisetron 20 μg kg^{-1} (n=30)	Granisetron 40 μg kg^{-1} (n=30)	Granisetron 100 μg kg^{-1} (n=30)
Age (yr)	44.6 (22–65)	43.8 (23–68)	44.0 (22–65)	42.0 (22–66)
Height (cm)	157.0 (6.8)	157.6 (7.0)	156.4 (5.5)	155.9 (6.3)
Weight (kg)	54.9 (7.3)	55.9 (6.6)	56.2 (8.2)	53.7 (8.0)
Duration of operation (min)	211.7 (38.1)	216.5 (43.1)	214.8 (38.1)	214.4 (39.9)
Duration of anaesthesia (min)	243.5 (40.4)	247.2 (44.9)	243.2 (38.2)	240.5 (39.2)
Indomethacin used postoperatively (n)	17	17	16	16
Types of operation performed (n)				
Tympanoplasty	23	22	22	22
Mastoidectomy	7	8	8	8

Table 2 Number (%) of patients having complete response (no PONV, no rescue antiemesis), and also nausea, retching, vomiting or requiring rescue antiemetic during the first 3 h (0–3 h) and the next 21 h (3–21 h) after anaesthesia. PONV=postoperative nausea and vomiting. *P* values *vs* placebo

	Placebo (n=30)	Granisetron 20 μg kg^{-1} (n=30)	*P*	Granisetron 40 μg kg^{-1} (n=30)	*P*	Granisetron 100 μg kg^{-1} (n=30)	*P*
0–3 h after anaesthesia							
Complete response (no PONV, no rescue antiemesis)	12 (40)	13 (43)	0.5	25 (83)	0.001	26 (87)	0.001
Nausea	9 (30)	8 (27)	0.5	3 (10)	0.052	3 (10)	0.052
Retching	1 (3)	2 (7)	0.5	0 (0)	0.5	1 (3)	1.0
Vomiting	8 (27)	7 (23)	0.5	2 (7)	0.04	1 (3)	0.013
Rescue antiemesis	6 (20)	5 (17)	0.5	0 (0)	0.012	0 (0)	0.012
3–24 h after anaesthesia							
Complete response (no PONV, no rescue antiemesis)	14 (47)	15 (50)	0.5	26 (87)	0.001	26 (87)	0.001
Nausea	7 (23)	7 (23)	1.0	2 (7)	0.073	2 (7)	0.073
Retching	1 (3)	1 (3)	1.0	0 (0)	0.5	1 (3)	1.0
Vomiting	8 (27)	7 (23)	0.5	2 (7)	0.04	1 (3)	0.013
Rescue antiemesis	5 (17)	5 (17)	1.0	0 (0)	0.026	0 (0)	0.026

Table 3 Adverse events. Values are number (%). No significant differences

	Placebo (n=30)	Granisetron 20 μg kg^{-1} (n=30)	Granisetron 40 μg kg^{-1} (n=30)	Granisetron 100 μg kg^{-1} (n=30)
0–3 h after anaesthesia				
Any adverse effects	6 (20)	6 (20)	5 (17)	5 (17)
Headache	2 (7)	2 (7)	2 (7)	2 (7)
Dizziness	2 (7)	2 (7)	2 (7)	2 (7)
Others (constipation, muscle pain)	2 (7)	2 (7)	1 (3)	1 (3)
3–24 h after anaesthesia				
Any adverse efects	6 (20)	5 (17)	5 (17)	6 (20)
Headache	3 (10)	2 (7)	2 (7)	3 (10)
Dizziness	2 (7)	2 (7)	2 (7)	2 (7)
Others (constipation, muscle pain)	1 (3)	1 (3)	1 (3)	1 (3)

antiemetic. Details of any adverse effects throughout the study were also recorded by a follow-up nurse who interviewed the patients.

Statistical analyses of data obtained were performed by one-way analysis of variance (ANOVA) with Bonferroni correction for multiple comparison, the chi-square test or Fisher's exact probability test, as appropriate. $P<0.05$ was considered significant. All values were expressed as mean (SD), median (ranges) or number (%). We set $\alpha=0.05$ and $\beta=0.8$, and used a large magnitude of effect (effective size 0.8) to estimate a sufficient sample size. The analysis showed that 30 patients per group would be sufficient.

Results

The treatment groups were comparable with regard to patient characteristics and types of operation (table 1).

During 0–3 h after anaesthesia, a complete response occurred in 12 of 30 patients (40%) who had received placebo *vs* 13 of 30 patients (43%) who had received granisetron 20 μg kg^{-1} (P=0.5), 25 of 30 (83%) who had received granisetron 40 μg kg^{-1} (P=0.001), and 26 of 30 (87%) who had received granisetron 100 μg kg^{-1} (P=0.001). During 3–24 h after anaesthesia, these data were 14 of 30 (47%) with placebo *vs* 15 of 30 (50%) with granisetron 20 μg kg^{-1} (P=0.5), 26 of 30 (87%) with granisetron 40μg kg^{-1} (P=0.001), and 26 of 30 (87%) with granisetron 100 μg kg^{-1} (P=0.001) (table 2).

The most common adverse events in the four groups were headache and dizziness (table 3). There were no differences in the incidence of these events during the first 3 h and the next 21 h after anaesthesia among the treatment groups (that is, the incidence was 17–20% in each group).

Discussion

Middle-ear surgery (tympanoplasty or mastoidectomy) is associated with a relatively high incidence of PONV.[1-3] Previous studies found the incidence of PONV to be between 62% and 80% in patients undergoing general anaesthesia for middle-ear surgery.[1–3] The incidence of PONV (no complete response) in this study was approximately 60% in patients who had received placebo, and was in accordance with our previous study in this population.[6]

The aetiology of PONV after middle-ear surgery is complex and depends on several factors, which include patient characteristics, types of surgery, anaesthetic technique and postoperative pain.[7] Patient-related factors are age, sex, obesity and a history of motion sickness or previous PONV or both. Surgical factors include an increased middle-ear pressure caused by nitrous oxide.[3] In the present study, however, the treatment groups were comparable with respect to patient characteristics, surgical procedure, anaesthetics administered and analgesics used after operation. In addition, no pressure was generated in the middle-ear from diffusion of nitrous oxide, which was replaced by air before closing of tympanic membrane. Therefore, the difference in the incidence of PONV among the groups can be attributed to the difference in dose of granisetron administered. Granisetron has been reported to be effective for the treatment of emesis induced by cancer chemotherapy.[4] In previous studies we have demonstrated that granisetron 40 $\mu g\ kg^{-1}$ reduces the incidence of PONV after middle-ear surgery and gynaecological surgery.[6 8]

For the treatment of emesis induced by cancer therapy, the effective dose of granisetron is between 40 $\mu g\ kg^{-1}$ and 80 $\mu g\ kg^{-1}$.[9] We demonstrated in the present study that granisetron 40 $\mu g\ kg^{-1}$ was as effective as granisetron 100 $\mu g\ kg^{-1}$ in the prevention of PONV, and that antiemetic efficacy of each dose was superior to that of placebo during the periods 0–3 h and 3–24 h (P=0.001). No difference in a complete response (no PONV, no rescue) was observed between patients who had received placebo and those who had received granisetron 20 $\mu g\ kg^{-1}$. These results suggest that granisetron 40 $\mu g\ kg^{-1}$ is the minimum effective dose for the prevention of PONV after middle-ear surgery. Adverse events observed in this study were relatively mild, and there was no difference in the incidence of adverse effects, such as headache and dizziness, among the four groups.

The use of new antiemetics (for example, 5-HT$_3$ receptor antagonists) has been recently criticized because of its high cost.[10] Our hospital pharmacy pays $103 for granisetron 3 mg, and the drug is much more expensive than other antiemetics (for example, $1.8 for droperidol 2.5 ma, $0.6 for metoclopramide 10 mg). However, use of these cheaper antiemetics has been limited because of their side effects, which include excessive sedation and extra pyramidal symptoms.[7] Furthermore, on the basis of our results, the use of a lower dose (40 $\mu g\ kg^{-1}$) would reduce the cost of granisetron. In conclusion, granisetron 40 $\mu g\ kg^{-1}$ is an effective antiemetic for the prevention of PONV after middle-ear surgery. Increasing the dose to 100 $\mu g\ kg^{-1}$ provides no demonstrable benefit in reducing the incidence of PONV.

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Respiratory complications associated with tracheal intubation and extubation†

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Summary

We conducted a prospective survey on the incidence of respiratory complications associated with tracheal intubation and extubation in 1005 patients who underwent elective general anaesthesia over a 4-month period. During induction of anaesthesia respiratory complications occurred in 46 patients (4.6%; 95% confidence limits (CL): 3.3, 5.9%). The common complications were coughing (1.5%) and difficult ventilation through a facemask (1.4%). Tracheal intubation was difficult in eight patients (0.8%). Complications occurred immediately after tracheal extubation in 127 patients (12.6%; 95% CL: 10.6, 14.7) and in the recovery room in 95 patients (9.5%; 95% CL: 7.6, 11.3%). The common complications immediately after extubation were coughing (6.6%) and oxygen desaturation (Sa_{O_2} < 90%) (2.4%), and in the recovery room, airway obstruction (3.8%) and coughing (3.1%). The incidence of complications was significantly higher immediately after tracheal extubation than during induction of anaesthesia ($P << 0.001$). Even when all incidents of coughing that occurred after tracheal extubation were disregarded as a complication, the overall incidence was still higher immediately after extubation (7.4%) than during induction of anaesthesia ($P < 0.01$). We conclude that the incidence of respiratory complications associated with tracheal extubation may be higher than that during tracheal intubation. (*Br. J. Anaesth.* 1998; **80**: 767–775)

Keywords: complications extubation tracheal; complications intubation tracheal; complications respiratory incidence

The prediction, incidence and mechanisms of difficult tracheal intubation have been extensively studied.[1–5] The incidence and detection of inadvertent oesophageal intubation have also been reported.[6 7] However, the incidence of other respiratory complications that occur during induction of anaesthesia has not been studied.

Respiratory complications may be frequent during and after tracheal extubation.[8 9] There have been several reports of the incidence of respiratory complications occurring in the recovery room,[10–15] but we have found no comprehensive report of the incidence of complications immediately after tracheal extubation.

The main aims of the present study were therefore to establish the incidence of respiratory complications during induction of anaesthesia, and during and after emergence from anaesthesia, and to examine if some factors, such as difference in sex, age, ease of laryngoscopy or depth of anaesthesia during tracheal extubation, influenced the incidence of respiratory complications.

Patients and methods

We conducted a prospective survey to ascertain the incidence of respiratory complications associated with tracheal intubation and extubation. The chairman of the local Ethics Committee informed us that, because of the nature of the study, submission of a protocol to the Committee was unnecessary. The study was carried out at the main operating theatres of the University Hospital of Wales, where about 12 000 surgical cases are dealt with each year; no obstetric, orthopaedic or thoracic surgery was performed, nor was there any day surgery.

In a preliminary unpublished study, we obtained data for about 250 patients on respiratory complications that occurred during emergence from anaesthesia. On the basis of these findings, we developed a formal data-recording form (fig. 1)and estimated the required number of patients for analysis. Data from this preliminary study were not included in the analysis.

We attempted to obtain data from all patients who underwent elective surgery, in whom the trachea was intubated and extubated in the operating theatre. After operation patients were transferred to the recovery room while oxygen 6 l min^{-1} was supplied through a Hudson facemask; in the recovery room, their condition was monitored by recovery nurses, who decided when to discharge patients to the ward. Data were not obtained when patients were transferred directly to the intensive care unit or when tracheostomy was performed before or during operation.

The incidence of difficult tracheal intubation is reported to be less than 2%,[6 10 16 17] and that of laryngospasm to be less than 1%.[6 10 17 18] The incidence of oesophageal intubation would also be less than 1%.[6] Therefore we estimated that the incidence of respiratory complications during induction of anaes-

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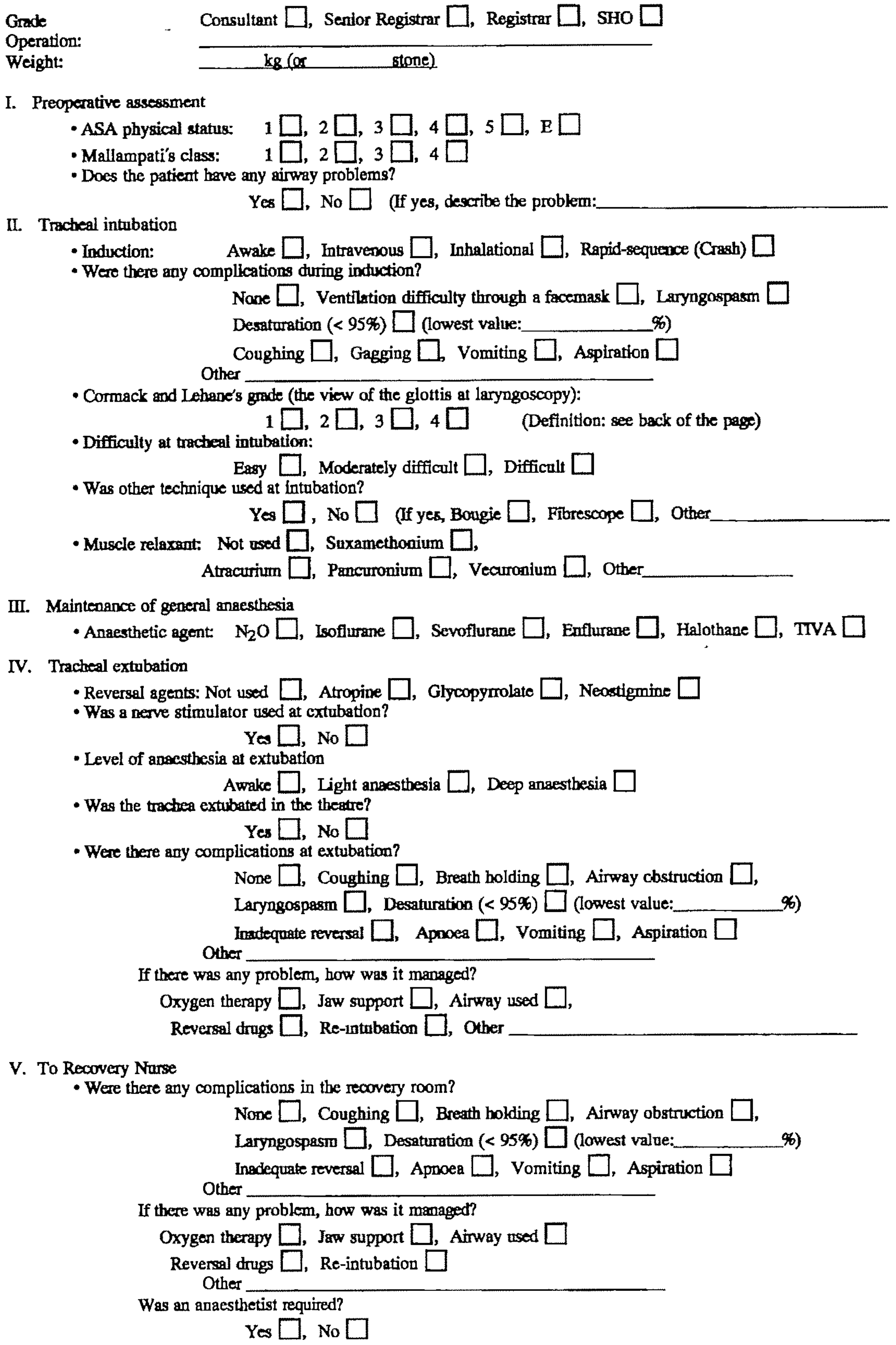

Grade Consultant ☐, Senior Registrar ☐, Registrar ☐, SHO ☐
Operation: ______________________________
Weight: ________kg (or ________stone)

I. Preoperative assessment
- ASA physical status: 1 ☐, 2 ☐, 3 ☐, 4 ☐, 5 ☐, E ☐
- Mallampati's class: 1 ☐, 2 ☐, 3 ☐, 4 ☐
- Does the patient have any airway problems?
  Yes ☐, No ☐ (If yes, describe the problem:______________________

II. Tracheal intubation
- Induction: Awake ☐, Intravenous ☐, Inhalational ☐, Rapid-sequence (Crash) ☐
- Were there any complications during induction?
  None ☐, Ventilation difficulty through a facemask ☐, Laryngospasm ☐
  Desaturation (< 95%) ☐ (lowest value:____________%)
  Coughing ☐, Gagging ☐, Vomiting ☐, Aspiration ☐
  Other ______________________________
- Cormack and Lehane's grade (the view of the glottis at laryngoscopy):
  1 ☐, 2 ☐, 3 ☐, 4 ☐ (Definition: see back of the page)
- Difficulty at tracheal intubation:
  Easy ☐, Moderately difficult ☐, Difficult ☐
- Was other technique used at intubation?
  Yes ☐, No ☐ (If yes, Bougie ☐, Fibrescope ☐, Other________________
- Muscle relaxant: Not used ☐, Suxamethonium ☐,
  Atracurium ☐, Pancuronium ☐, Vecuronium ☐, Other______________

III. Maintenance of general anaesthesia
- Anaesthetic agent: N_2O ☐, Isoflurane ☐, Sevoflurane ☐, Enflurane ☐, Halothane ☐, TIVA ☐

IV. Tracheal extubation
- Reversal agents: Not used ☐, Atropine ☐, Glycopyrrolate ☐, Neostigmine ☐
- Was a nerve stimulator used at extubation?
  Yes ☐, No ☐
- Level of anaesthesia at extubation
  Awake ☐, Light anaesthesia ☐, Deep anaesthesia ☐
- Was the trachea extubated in the theatre?
  Yes ☐, No ☐
- Were there any complications at extubation?
  None ☐, Coughing ☐, Breath holding ☐, Airway obstruction ☐,
  Laryngospasm ☐, Desaturation (< 95%) ☐ (lowest value:__________%)
  Inadequate reversal ☐, Apnoea ☐, Vomiting ☐, Aspiration ☐
  Other ______________________________

  If there was any problem, how was it managed?
  Oxygen therapy ☐, Jaw support ☐, Airway used ☐,
  Reversal drugs ☐, Re-intubation ☐, Other ______________________________

V. To Recovery Nurse
- Were there any complications in the recovery room?
  None ☐, Coughing ☐, Breath holding ☐, Airway obstruction ☐,
  Laryngospasm ☐, Desaturation (< 95%) ☐ (lowest value:__________%)
  Inadequate reversal ☐, Apnoea ☐, Vomiting ☐, Aspiration ☐
  Other ______________________________

  If there was any problem, how was it managed?
  Oxygen therapy ☐, Jaw support ☐, Airway used ☐
  Reversal drugs ☐, Re-intubation ☐
  Other ______________________________

  Was an anaesthetist required?
  Yes ☐, No ☐

Figure 1 Data-recording form. Some sections (title; date; definition and figures for the view of the oropharynx and the glottis) are omitted here.

thesia would be up to 5%. In the preliminary observations of 250 patients, the incidence of complications after tracheal extubation was 10–15%. To detect this difference in incidence of complications at the times of induction of anaesthesia and extubation, with $P < 0.05$ and a power of 90%, 500–1000 patients would be required.[19]

DATA-RECORDING FORM

The data-recording form was designed to fit on both sides of a sheet of A4 paper (fig. 1), and had five main sections, to record: (I) information obtained at preoperative assesment; (II) details about induction of anaesthesia; (III) methods by which generalanaesthesia was maintained; (IV) details about tracheal

Table 1 Relationship between preoperative view of the oropharynx and view of the glottis at laryngoscopy. Data from 858 patients are shown; the view of the oropharynx was not examined in the remaining 147 patients (see text). *In 15 patients the trachea was intubated without the use of a laryngoscope (fibrescope-aided tracheal intubation)

	View of the glottis					
View of the oropharynx	Grade 1 (*n*, %)	Grade 2 (*n*, %)	Grade 3 (*n*, %)	Grade 4 (*n*, %)	Not examined* (*n*, %)	Total (*n*, %)
Class 1	472	58	9	0	7	546 (63.6)
Class 2	121	82	33	1	6	243 (28.3)
Class 3	20	17	20	2	1	60 (7.0)
Class 4	2	2	4	0	1	9 (1.0)
Total	615 (71.7)	159 (18.5)	66 (7.7)	3 (0.3)	15 (1.7)	858 (100.0)

extubation; (V) respiratory complications and treatments that occurred in the recovery room.

The view of the oropharynx was classified according to Mallampati and colleagues[1] and Samsoon and Young[20]; the view of the glottis at laryngoscopy was graded according to Cormack and Lehane.[21] Definitions and schematic diagrams were provided for classification of the view of the oropharynx and of the glottis, because anaesthetists' understanding of the scoring is not always accurate.[22] No definition was provided for difficult ventilation through a facemask or difficult tracheal intubation, and no grading of the degree of difficulty in ventilation through a facemask was required.

The anaesthetists were asked to fill in the first four sections and the recovery nurses the last section. Each section required a tick in at least one box; for example, the section for complications included a box "None". This enabled us to detect errors of omission (no tick in any box) and commission (ticks in the "None" box and in a complication box); errors were rectified after collection of the data sheet (see below).

DATA COLLECTION

We aimed to collect data from 1000 patients and estimated that this would take about 4 months. The study was done during the elective lists on Mondays to Fridays between November 4, 1996 and March 10, 1997; however, data were not collected between December 20 and January 5 because of the possibility of irregular lists during this period. Data collection was not carried out when no investigator could check the data sheets on the day of collection.

Table 2 Ranked incidence of preoperative problems of the airway. *Down's syndrome, Pierre Robin sequence (previously called Pierre Robin syndrome) and acromegaly

Problem	*n* (%)
Difficult view of the oropharynx	69 (6.9)
Limited extension of the neck	17 (1.7)
Asthma	14 (1.4)
Obstructed nasal passage	12 (1.2)
Fragile or protrusive teeth	10 (1.0)
Hoarseness	9 (0.9)
Short neck	6 (0.6)
Deviation of the trachea	5 (0.5)
Limited opening of the mouth	4 (0.4)
Receding jaw	3 (0.3)
Gastro-oesophageal reflux	3 (0.3)
Anomalies* with suspected difficult airway	3 (0.3)
Previous difficult intubation	2 (0.2)
History of tracheostomy	2 (0.2)
Cleft lip and palate	2 (0.2)
Vocal cord palsy	2 (0.2)
Oropharyngeal cyst	1 (0.1)
Bronchopulmonary dysplasia	1 (0.1)
Total (one or more problems)	145 (14.4)

Before the start of the survey, the aims were explained to each anaesthetist and recovery nurse. The method of completing the data sheet was also explained. Anaesthetists and nurses were able to refuse to participate; they were also able to refuse to collect a part of the data if they had objections — this occurred only for preoperative assessment of the view of the oropharynx (see Results).

An investigator handed data sheets to each anaesthetist before each morning and afternoon list to minimize omission of patients. When the patient was transferred to the recovery room after the operation, an investigator ensured that the data sheet was handed to the recovery nurse. When the nurse had completed the data sheet, the investigator collected it and checked the sheet. If there were omissions — except for body weight (see below) — the investigator contacted the anaesthetist or nurse involved as soon as possible on the same day and rectified the omissions.

The total number of patients admitted to the operating theatre and transferred to the recovery room was obtained from (1) a registration list that records all patients who have been transferred to the recovery room, and (2) a computer recording system[23] that stores all anaesthetic records submitted to our department. The numbers of patients for each type of anaesthesia (general, regional, local) and each method of airway management (for example, tracheal intubation, use of laryngeal mask airway) were obtained from the anaesthetic records.

DATA ANALYSIS

The proportions in each grade, category or type for the following factors were recorded: sex, age group, ASA physical status, grade of anaesthetist, type of operation, type of anaesthesia (general, regional or local), type of airway (for example, a tracheal tube or laryngeal mask), view of the oropharynx, view of the glottis, difficulty in tracheal intubation, type of anaesthetic agent, type of neuromuscular blocking agent, and depth of anaesthesia at tracheal extubation.

The incidence of respiratory complications during the following three periods was obtained: (1) induction of anaesthesia; (2) immediately after tracheal extubation (in the operating theatre); (3) shortly after extubation (during transfer of the patients from the operating theatre to the recovery room and in the recovery room).

Table 3 Ranked incidence of respiratory complications associated with tracheal intubation and extubation in 1005 patients

Complications occurring during induction of anaesthesia	*n* (%)	Complications occurring immediately after extubation (in operating theatre)	*n* (%)	Complications occurring shortly after extubation (in recovery room)	*n* (%)
Coughing	15 (1.5)	Coughing	66 (6.6)	Airway obstruction	38 (3.8)
Difficult ventilation	14 (1.4)	Desaturation (Sp_{O_2}<90%)	24 (2.4)	Coughing	31 (3.1)
Desaturation (Sp_{O_2}<90%)	11 (1.1)	Breath-holding	20 (2.0)	Desaturation (Sp_{O_2}<90%)	22 (2.2)
Difficult intubation	8 (0.8)	Airway obstruction	19 (1.9)	Laryngospasm	8 (0.8)
Laryngospasm	4 (0.4)	Laryngospasm	17 (1.7)	Apnoea, hypoventilation	8 (0.8)
Oesophageal intubation	3 (0.3)	Apnoea, hypoventilation	9 (0.9)	Vomiting	7 (0.7)
Gagging	1 (0.1)	Inadequate reversal	5 (0.5)	Breath-holding	3 (0.3)
		Vomiting	3 (0.3)	Inadequate reversal	3 (0.3)
		Masseter spasm	1 (0.1)	Bronchospasm	2 (0.2)
Patients experiencing one or more complication	46 (4.6)		126 (12.5)		95 (9.5)
95% confidence limits	3.3, 5.9%		10.5, 14.6%		7.6, 11.3%

The view of the oropharynx was defined as difficult when classed as 3 or 4.[5 20] Laryngoscopy was defined as difficult when the view of the glottis was graded 3 or 4.[3 24] Difficulty in laryngoscopy was not regarded as a complication unless tracheal intubation was difficult; difficulty with tracheal intubation was regarded as a complication only when anaesthetists recorded it as "difficult" (that is, not moderately difficult or easy).

STATISTICAL ANALYSIS

The chi-square test for trend was used to test the relationship between ease of viewing the glottis with the quality of the preoperative view of the oropharynx, in terms of the view of the oropharynx (classes 1 and 2) *vs* obscured view (classes 3 and 4). Grades 3 and 4 of the view of the glottis were also pooled to avoid expected frequencies of less than 5.[25]

Fisher's exact test was used to compare the total incidence of complications occurring during induction of anaesthesia with that immediately after tracheal extubation. No hypothesis test was used for complications that occurred shortly after tracheal extubation, as these included occurrence over a considerably longer period than the other two circumstances. $P < 0.05$ was considered significant. If the P was much smaller than 0.001, it was expressed as $P << 0.001$.

The 95% confidence limits (CL) for the incidences of complications at each period were calculated.[26] For respiratory complications during induction of anaesthesia and after tracheal extubation, the relative risk and 95% CL were calculated for the following predetermined set of factors: sex difference, age difference (15 yr or younger *vs* older), ASA physical status (I and II *vs* III and IV), the grade of anaesthetist (consultants and senior registrars *vs* registrars and senior house officers), the view of the oropharynx (classes 1 and 2 *vs* 3 and 4), the presence or absence of preoperative airway problems, and depth of anaesthesia during tracheal extubation (deep *vs* awake). We could not obtain accurate data for patients' weight and height, because they were not routinely measured before operation; therefore it was not possible to classify patients as obese or non-obese. Nevertheless, we arbitrarily classified patients of 16 yr or older into two groups (90 kg or heavier and less than 90 kg) and included this factor in the analysis.

Results

DATA COLLECTION, TYPE OF ANAESTHESIA AND PATIENT CHARACTERISTICS

Sixty five of 68 anaesthetists who were working at the main operating theatres during the study period agreed to participate in the study.

During the 4-month period, 1774 patients underwent elective surgery and were admitted to the recovery room. The trachea was intubated in 1200 patients, who were the subjects for data collection. Data for 1011 patients were obtained, but six sets of data were withdrawn from the analysis because of omissions not detected by an investigator on the day of collection. Therefore 1005 data sets were used for analysis (collection rate: 83.8%).

PREOPERATIVE AIRWAY PROBLEMS

During the preoperative period, no view of the oropharynx was obtained in 147 patients (14.6%), because it was the policy of the anaesthetist or because the patient was too young to co-operate (for

Table 4 Ease of tracheal intubation related to grade of view of the glottis at laryngoscopy and in patients in whom other techniques were used for tracheal intubation

Technique (no. of patients)	Easy *n* (%)	Moderately difficult *n* (%)	Difficult *n* (%)
Laryngoscopy (*n*=958)			
Grade 1 (*n*=693)	678 (67.5)	15 (1.5)	0
Grade 2 (*n*=194)	149 (14.8)	45 (4.5)	0
Grade 3 (*n*=68)	13 (1.3)	50 (5.0)	5 (0.5)
Grade 4 (*n*=3)	1 (0.1)	1 (0.1)	1 (0.1)
Fibreoptic bronchoscopy (*n*=45)	39 (3.9)	4 (0.4)	2 (0.2)
Retrograde method (*n*=1)	1 (0.1)	0	0
Blind nasal method (*n*=1)	1 (0.1)	0	0
Total (*n*=1005)	882 (87.8)	115 (11.4)	8 (0.8)

Table 5 Incidence of respiratory complications during induction of anaesthesia and after tracheal extubation in 1005 patients according to sex, age group, ASA physical status, grade of anaesthetist, view of oropharynx and presence or absence of preoperative airway problems, and incidence of complications during emergence from anaesthesia according to anaesthetic method, muscle relaxant and level of anaesthesia at tracheal extubation. †Includes patients aged 16 yr or older whose weights were described. ‡Does not include patients in whom view of the oropharynx was grade 3 or 4 but no other airway problems were found. *Indicates marked differences between groups (see table 6). CL, confidence limits

		Complications during emergence from anaesthesia		
Factors	Complications during induction of anaesthesia *n* (%) (95% CL)	Immediately after extubation *n* (%)	Shortly after extubation *n* (%)	Total of either or both *n* (%) (95% CL)
Sex				
Male (*n*=457)	28 (6.1) (3.9, 8.3)*	62 (13.6)	50 (10.9)	103 (22.5) (18.7, 26.4)*
Female (*n*=548)	18 (3.3) (1.8, 4.8)*	64 (11.7)	45 (8.2)	97 (17.7) (14.5, 20.9)*
Age (yr)				
<1 (*n*=28)	2 (7.1) (0, 16.7)	1 (3.6)	0	1 (3.6) (0, 10.4)
1–9 (*n*=37)	2 (5.4) (0, 12.7)	7 (18.9)	3 (8.1)	10 (27.0) (12.7, 41.3)
10–15 (*n*=31)	1 (3.2) (0, 9.4)	1 (3.2)	2 (6.5)	3 (9.7) (0, 20.0)
16–19 (*n*=33)	1 (3.0) (0, 8.9)	4 (12.1)	4 (12.1)	8 (24.2) (9 6, 38.9)
20–39 (*n*=234)	6 (2.6) (0.5, 4.6)	35 (15.0)	20 (8.5)	52 (22.2) (16.9, 27.5)
40–59 (*n*=327)	17 (5.2) (2.8, 7.6)	46 (14.1)	35 (10.7)	70 (21.4) (17.0, 25.9)
60–79 (*n*=279)	17 (6.1) (3.3, 8.9)	31 (11.1)	28 (10.0)	52 (18.6) (14.1, 23.2)
≥80 (*n*=36)	0	1 (2.8)	3 (8.3)	4 (11.1) (0 8, 21.4)
Weight (kg)†				
<90 (*n*=726)	22 (3.0) (1.8, 4.3)*	86 (11.8)	69 (9.5)	140 (19.3) (16.4, 22.2)
≥90 (*n*=137)	14 (10.2) (5.1, 15.3)*	27 (19.7)	16 (11.7)	37 (27.0) (19.6, 34.4)
ASA physical status				
I or II (*n*=772)	33 (4.3) (2.8, 5.7)	95 (12.3)	67 (8.7)	151 (19.6) (16.8, 22.4)
III or IV (*n*=233)	13 (5.6) (2.6, 8.5)	31 (13.3)	28 (12.0)	49 (21.0) (15.8, 26.3)
Grade of anaesthetist				
Consultant (*n*=576)	25 (4.3) (2.7, 6.0)	66 (11.5)	63 (10.9)	112 (19.4) (16.2, 22.7)
Senior registrar (*n*=228)	9 (3.9) (1.4, 6.5)	27 (11.8)	20 (8.8)	44 (19.3) (14.2, 24.4)
Registrar or senior house officer (*n*=201)	12 (6.0) (2.7, 9.2)	33 (16.4)	12 (6.0)	44 (21.9) (16.2, 27.6)
Preoperative view of the oropharynx				
Clear (grade 1+2) (*n*=789)	23 (2.9) (1.7, 4.1)*	94 (11.9)	69 (8.7)	149 (18.9) (16.2, 21.6)
Obscure (grade 3+4) (*n*=69)	10 (14.5) (6.2, 22.8)*	10 (14.5)	9 (13.0)	16 (23.2) (13.2, 33.1)
Preoperative airway problems‡				
Present (*n*=94)	12 (12.8) (6.0, 19.5)*	14 (14.9)	10 (10.6)	20 (21.3) (13.0, 29.6)
Absent (*n*=911)	34 (3.7) (2.5, 5.0)*	112 (12.3)	85 (9.3)	180 (19.8) (17.2, 22.3)
Anaesthetic method				
Isoflurane (*n*=792)	—	93 (11.7)	77 (9.7)	153 (19.3) (16.6, 22.1)
Sevoflurane (*n*=108)	—	19 (17.6)	4 (3.7)	22 (20.4) (12.8, 28.0)
Enflurane (*n*=73)	—	12 (16.4)	10 (13.7)	21 (28.8) (18.4, 33.2)
Total intravenous anaesthesia (*n*=32)	—	2 (6.3)	4 (12.5)	4 (12.5) (1.0, 24.0)
Muscle relaxant used during operation				
Not used (*n*=8)	—	1 (12.5)	1 (12.5)	1 (12.5) (0, 35.4)
Suxamethonium (*n*=55)	—	8 (14.5)	13 (23.6)	19 (34.5) (22.0, 47.1)
Vecuronium (*n*=544)	—	61 (11.2)	42 (7.7)	96 (17.6) (14.4, 20 9)
Atracurium (*n*=344)	—	45 (13.1)	35 (10.2)	71 (20.6) (16.4, 24.9)
Rocuronium (*n*=42)	—	9 (21.4)	4 (9.5)	11 (26.2) (12.9, 39.5)
Pancuronium (*n*=12)	—	2 (16.7)	0	2 (16.7) (0, 37.8)
Level of anaesthesia at tracheal extubation				
Deep (*n*=202)	—	36 (17.8)	32 (15.8)	60 (29.7) (23.4, 36.0)*
Light (*n*=348)	—	44 (12.6)	31 (8.9)	70 (20.1) (15.9, 24.3)
Awake (*n*=455)	—	46 (10.1)	32 (7.0)	70 (15.4) (12.1, 18.7)*
Total (*n*=1005)	46 (4.6) (3.3, 5.9)	126 (12.5)	95 (9.5)	200 (19.9) (17.4, 22.4)

example, infants). In the remaining 858 patients, the view of the oropharynx was difficult (class 3 or 4) in 69 patients (8%) (table 1). In total, airway problems were noted in 145 of 1005 patients (14.4%) before operation (table 2).

COMPLICATIONS DURING INDUCTION OF ANAESTHESIA

Respiratory complications occurred in 46 of 1005 patients (4.6%) during induction of anaesthesia (table 3).

Difficulty in ventilation through a facemask

Ventilation through a facemask was difficult in 14 of 1005 patients (1.4%). In six of these 14 patients, airway problems were detected before induction of anaesthesia (class 3 view of the oropharynx; limited movement of the head and neck; short neck and obstruction of the nasal passage). Desaturation occurred in two of 14 patients (arterial haemoglobin oxygen saturation 85 and 65%, respectively), in one of whom an airway problem ("short neck") was recognized before anaesthesia. A retrograde method was used in one patient, because a difficult tracheal intubation had been predicted preoperatively (limited extension of the head and neck); in spite of difficult ventilation through a facemask, retrograde tracheal intubation succeeded within a few minutes without causing hypoxaemia. A laryngoscope was used for tracheal intubation in the remaining 13 patients, and laryngoscopy was difficult in only two patients (grade 3 in each case).

Difficulty in laryngoscopy and tracheal intubation

Laryngoscopy was difficult (grade 3 or 4) in 71 of 958 patients (7.4%) (table 4), but desaturation occurred in only two of them. In 32 of these 71 patients, airway problems were identified before

Table 6 Relative risks for factors for which the lower limit of 95% confidence intervals is equal to or greater than 1.0. †Includes patients aged 16 yr or older whose weights were described. ‡Does not include patients in whom the view of the oropharynx was class 3 or 4 but no other airway problems were found

	Relative risk of respiratory complications	
Factor	Induction of anaesthesia	Emergence from anaesthesia
Sex (male/female)	1.9 [1.1, 3.3]	1.3 [1.0, 1.6]
Weight† (≥90 kg/<90 kg)	3.4 [1.8, 6.4]	—
Preoperative view of the oropharynx (clear (class 1 or 2)/obscure (3 or 4))	5.0 [2.5, 10.0]	—
Preoperative airway problems‡ (present/absent)	3.8 [2.2, 6.7]	—
Depth of anaesthesia at tracheal extubation ("deep"/awake)	—	1.9 [1.4, 2.6]

Table 7 Incidence of one or more respiratory complications after tracheal extubation according to level of anaesthesia at tracheal extubation and type of operation

	No. of patients experiencing respiratory complications			
Type of operation	Awake (*n*, %)	Light anaesthesia (*n*, %)	Deep anaesthesia (*n*, %)	Total no.
Neurosurgery (*n*=176)	6/70 (8.6)	11/38 (28.9)	21/68 (30.9)	38/176 (21.6)
Eye, ear, nose and throat, dental (*n*=293)	30/126 (23.8)	20/101 (19.8)	23/66 (34.8)	73/293 (24.9)
Neck and breast (*n*=134)	8/56 (14.3)	9/46 (19.6)	9/32 (28.1)	26/134 (19.4)
Abdominal, renal and major vascular (*n*=278)	16/129 (12.4)	21/125 (16.8)	4/24 (16.7)	41/278 (14.7)
Genitourinary, perineal and others (*n*=124)	10/74 (13.5)	9/38 (23.7)	3/12 (25.0)	22/124 (17.7)
Total (*n*=1005)	70/455 (15.4)	70/348 (20.1)	60/202 (29.7)	200/1005 (19.9)

operation. Tracheal intubation was difficult in eight patients (0.8%) (table 3); difficulty had been predicted preoperatively in five of them.

In 117 patients in whom tracheal intubation using a laryngoscope was difficult or moderately difficult, the trachea was intubated without the aid of another device in 53 patients, and with the aid of a gum elastic bougie in the remaining 64 patients. Tracheal intubation was successful in all patients.

There was a significant association between the preoperative view of the oropharynx and the view of the glottis at laryngoscopy (chi-square test for trend: $P << 0.001$) (table 1).

Complications associated with fibrescope-aided tracheal intubation

A fibreoptic bronchoscope was used for tracheal intubation in 45 patients, of whom four experienced respiratory complications: coughing and gagging occurred in one patient, and desaturation in two anaesthetized and one sedated patient.

Oesophageal intubation

Oesophageal intubation occurred in three patients: tracheal intubation using a laryngoscope was moderately difficult in two of these patients and difficult in the third.

COMPLICATIONS AFTER TRACHEAL EXTUBATION

Respiratory complications occurred in 127 patients (12.6%) immediately after tracheal extubation and in 95 patients (9.5%) shortly after (table 3); overall, one or more respiratory complication occurred in 195 of 1005 patients (19.4%) after tracheal extubation.

The incidence of complications immediately after tracheal extubation was significantly higher than that during induction of anaesthesia ($P << 0.001$).

FACTORS THAT AFFECT RESPIRATORY COMPLICATIONS

The incidence of respiratory complications for each factor is shown in detail in table 5. The relative risks with 95% confidence limits (table 6) showed that a few factors significantly affected the incidence of respiratory complications (CL for the relative risk exceeded 1.0) during induction of, or emergence from, anaesthesia. First, during both induction of anaesthesia and emergence from anaesthesia, the risks were greater in males than in females. Second, as expected, during induction of anaesthesia the risk of respiratory complications was greater when the view of the oropharynx was not clear or airway problems were found preoperatively; however, during emergence from anaesthesia, this factor did not affect the risk of complications (table 6). Third, the risk was greater in patients who were 90 kg or heavier than in those who were lighter than 90 kg. Last, complications were more likely if the trachea was extubated while the patient was still deeply anaesthetized rather than after the patient had regained consciousness (table 6).

The last difference might have reflected different populations between these two groups (awake *vs* deep). However, this seems unlikely, as the incidence of complications after tracheal extubation was generally greater in anaesthetized patients than awake patients, regardless of the type of operation (table 7).

Discussion

COMPLICATIONS DURING INDUCTION OF ANAESTHESIA

Several complications occurred during induction of anaesthesia, the incidence of each being up to 1.5%.

Difficulty in ventilation through a facemask, which could be life-threatening, was as frequent as difficulty in tracheal intubation during induction of anaesthesia (table 3). As with previous studies,[1 3-5] the incidence of difficult laryngoscopy or difficult tracheal intubation was significantly higher when it was difficult to see the oropharynx clearly preoperatively (table 1). In eight patients in whom tracheal intubation was difficult, airway problems were detected in five patients before induction of anaesthesia. However, in more than 50% of patients in whom ventilation through a facemask was difficult, no airway problems had been detected before induction of anaesthesia.

COMPLICATIONS AFTER TRACHEAL EXTUBATION

Respiratory complications were considerably more frequent immediately after tracheal extubation than during induction of anaesthesia (table 3). The most common was coughing (6.6%), but potentially serious complications, such as desaturation and laryngospasm, also occurred more often than during induction of anaesthesia (table 3).

Coughing is usually not a complication in itself, as it is a physiological response to protect the airway from aspiration. However, coughing may increase arterial pressure, heart rate and intraocular or intracranial pressure,[27 28] and ineffective or persistent coughing might be associated with complications such as laryngospasm. It may be reasonable to regard coughing as a complication if other complications, such as decrease in Sp_{O_2}, laryngospasm or airway obstruction, are associated with coughing. In the present study, coughing was associated with other respiratory complications in 13 of 66 patients (20%) immediately after tracheal extubation and in 5 of 31 patients (16%) shortly after tracheal extubation. Nevertheless, even when all postoperative coughing is disregarded as a complication, the overall incidence of respiratory complications is still considerably higher, both immediately after tracheal extubation (7.4%; 95% CL: 6.0, 9.3) or shortly after extubation (6.9%: 95% CL: 5.5, 8.6) than during induction of anaesthesia. The incidence immediately after tracheal extubation was still significantly higher than during induction ($P < 0.01$).

Surprisingly, the incidence of respiratory complications remained high in the recovery room (table 3). Airway obstruction, apnoea or laryngobronchospasm occurred more frequently after discharge from the operating theatre than during induction of anaesthesia.

FACTORS POSSIBLY AFFECTING COMPLICATIONS

Previous studies have shown that several factors affect the incidence of respiratory complications. In a series of 16 065 patients, the poorer the preoperative physical status, the higher the incidence of respiratory complications occurring in the recovery room.[12] Similarly, the older the patient, the greater the incidence of respiratory complications.[12] Another study showed that the incidence of respiratory complications in the recovery room is increased in males and in elderly patients, and after thoracic or abdominal surgery.[11]

In the present study, there were differences in the incidence of respiratory complications according to sex, presence or absence of preoperative airway problems, depth of anaesthesia at tracheal extubation, and weight (heavier or lighter than 90 kg) (table 6). The reasons for these differences in the incidence of complications, particularly the difference between the sexes, are not clear from the present study. Other factors that we did not analyse — smoking habit, history of upper respiratory infection and obesity (in the present study, we only distinguished between patients heavier or lighter than 90 kg) could have contributed to the difference in the incidence of respiratory complications between males and females.

In addition, several other differences in anaesthesia management, such as the use or the avoidance of nitrous oxide during operation or oxygen supply after tracheal extubation, could also alter the incidence of respiratory complications. We could not analyse these factors because nitrous oxide was used in all patients and oxygen was always supplied after tracheal extubation.

TIMING OF TRACHEAL EXTUBATION

Tracheal extubation under deep anaesthesia has been recommended for patients undergoing intracranial or intraocular operation or for those in whom an increase in arterial pressure could be detrimental.[8 9] This practice will reduce the incidence and degree of straining (bucking) or coughing and stimulation of on arterial or intraocular pressures. However, we have found that the incidence of other respiratory complications after tracheal extubation will be greater when the trachea is extubated while the patient is still deeply anaesthetized (table 6). This is true regardless of the type of operation (table 7), and still applies in the recovery room (table 5). Therefore, constant vigilance is required when the trachea is extubated while the patient is still deeply anaesthetized. Use of the laryngeal mask after tracheal extubation may be an alternative means by which to achieve "smooth extubation" and recovery.[29 30]

This result is consistent with a previous study, which showed that the more conscious the patient is on arrival at the recovery room, the lower the incidence of respiratory complications.[12] However, two studies in children reported that the incidence of desaturation was greater when the trachea was extubated after patients had regained consciousness rather than when they were still deeply anaesthetized.[31 32] In these studies there were no significant differences in the incidences of laryngospasm, coughing, breath-holding or airway obstruction,[31 32] but this may have been because too few patients were compared (beta error) (70 or 100 patients in total).[31 32] Future randomized, comparative studies of sufficient numbers of patients should clarify differences in the incidence of respiratory complications between these two modes of tracheal extubation.

MANAGEMENT OF POSTOPERATIVE RESPIRATORY COMPLICATIONS

During transfer of the patient from the operating theatre to the recovery room, and in the recovery room, there is a relative lack of monitors and equipment and anaesthetists are not always present. Once the patient has left the operating theatre, detection of complications may be delayed and prompt treatment may be more difficult. Several studies have shown that, during transfer from the operating theatre to the recovery room, arterial haemoglobin oxygen saturation often decreases,[35-37] even when oxygen is given.[34 35] It is advisable to give appropriate oxygen therapy routinely and to use a pulse oximeter during the transfer of the patient and in the recovery room.

There are well established procedures for the management of airway problems during induction of anaesthesia,[38] but no comprehensive guidelines for dealing with airway problems after tracheal extubation. We believe that dissemination of a simple algorithm for effective management of airway problems, such as one for laryngospasm,[39] is urgently required. Proper training of anaesthetists and recovery nurses in the management of postoperative respiratory complications on the basis of guidelines is also required.

The anaesthetist is responsible for the care of the patient from induction of anaesthesia to full recovery.[40] Our results support the recommendation that an anaesthetist with sufficient experience should be present in the recovery room, at least during normal operating hours.[41]

In summary, we have shown that the incidence of respiratory complications associated with tracheal extubation can be higher than that during tracheal intubation.

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Hospital mortality after urgent and emergency laparotomy in patients aged 65 yr and over. Risk and prediction of risk using multiple logistic regression analysis

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Summary

We studied 107 patients aged over 65 years undergoing urgent or emergency laparotomy. Aspects of preoperative assessment, perioperative management and postoperative care were analysed by multiple logistic regression to determine the factors that predicted hospital survival. We determined which factors influenced anaesthetists' prediction that patients would survive. These predictions were made both before and immediately after operation. The factors associated with the use of invasive cardiovascular monitoring were also studied. We obtained a model that accounted for 93% of the variability in the likelihood of survival. Age and ASA status were significant predictors of survival ($P < 0.05$), and of anaesthetists' prediction of mortality both before and after operation. Several other factors were significant determinants of survival but were not determinants of the anaesthetist's opinion regarding survival. (*Br. J. Anaesth.* 1998; **80**: 776–781)

Keywords: mortality risk factors; outcome prediction; surgery laparotomy emergency

Urgent or emergency laparotomy is a common procedure and has a mortality rate considerably greater than that of elective laparotomy.[1] In older patients abdominal pathology more often presents acutely,[2] and mortality is greater than in younger patients.[3] In one series 80% of perioperative surgical deaths were of elderly patients with abdominal pathology.[4]

As patients get older coincident diseases are more common. Even if there is no evidence of disease there may well be a decrease in physiological reserve (such as decreased glomerular filtration rate despite normal serum creatinine). The initial disease that requires surgery may be complicated by tissue hypoperfusion and acidosis from vomiting and loss of fluid into the gastrointestinal tract, or bleeding. Patients may be malnourished or cachectic after prolonged illness. Mortality rates are high (10–55%),[5–7] but comparison between series is difficult because of differing case mixes. Eighty-six percent of deaths reported in the National Confidential Enquiry into Perioperative Deaths (NCEPOD) were of patients aged over 60 yr and 57% of the reported deaths were after urgent or emergency operations.[8]

We conducted a pilot study of in-hospital mortality among a cohort of patients undergoing nonscheduled laparotomy in a district general hospital. We aimed to identify those patients at greatest risk and collect information prospectively to determine: (1) whether it is possible to predict who will die; (2) which factors predict outcome; (3) which factors influence decision making; and (4) whether these factors are the same.

Method

DATA COLLECTION

For a period of 6 months all patients at a district general hospital who underwent urgent or emergency laparotomy (NCEPOD definitions, fig. 1) entered the study. These patients were identified from emergency and elective surgical operation lists. Their management was not altered by being in the study. The senior anaesthetist treating the patient filled in a questionnaire (fig. 2) on preoperative assessment, perioperative management and postoperative care. The senior operating surgeon provided information where relevant. All information relating to preoperative assessment was collected before surgery. Before and immediately after surgery the surgeon and anaesthetist treating the patient were asked to predict patient outcome (whether or not the patient would leave hospital alive). Surgical opinion was collected by the anaesthetist completing the questionnaire without communicating his or her own opinion. Patient outcome and date of discharge from hospital or death were collected from the hospital's patient data system.

Time of operation (daytime, out of hours and night-time) was defined as NCEPOD uses the terms. ASA status was assigned by the anaesthetist according to the American Society of Anesthesiologists classification (fig. 3). Risk factors assessed before operation were summed to produce a risk factor score. Surgical procedures were classified as: (1) involving bowel resection, (2) not involving bowel resection or (3) repair of abdominal aortic aneurysm.

DATA ANALYSIS

The primary outcome measure was death in hospital. Data collected were subjected to multivariate analy-

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Emergency

Immediate life-saving operation, resuscitation simultaneous with surgical treatment. Operation usually within 1 h

Urgent

Operation as soon as possible after resuscitation. Operation within 24 h

Scheduled

An early operation, but not immediately life saving. Operation usually within 3 weeks

Elective

Operation at a time to suit both patient and surgeon

Figure 1 NCEPOD Classification of urgency of operation.

sis to determine those factors that predicted survival or death. In addition to this, we identified those factors that best explained anaesthetic and surgical opinions, before and after operation, of survival. A subsidiary analysis was also performed to determine the factors that explained the use of invasive cardiovascular monitoring. All the analyses were performed using the LOGIST procedure in SAS version 6.08 for Windows.

All the outcomes in this study were binary and were modelled using multiple logistic regression. This is a standard statistical procedure that determines the best possible explanation of a binary outcome in terms of the concerted effects of several potential variables (explanators) offered to the model. No assumptions are made about the distribution of the potential explanators. For all the models in this study a stepwise method of variable selection was used. This means that potential explanatory variables are added in turn to the model, starting with the variable with the most significant effect.

Date .... Patient name .... Consultant ....

Reg. number .... Age .... Ward ....

Time .... 08:00–17:59/18:00–24:00/00:01–07·59

PREOPERATIVE ASSESSMENT

Indication .... Grade of surgeon ....

Grade of anaesthetist .... Immediate preop ASA ....

Do you think the patient will leave hospital alive?	Yes/No
Does the surgeon?	Yes/No
Was the patient adequately resuscitated preoperatively?	Yes/No

PREOPERATIVE RISK FACTORS

Poor general condition	Y/N
Dehydration/hypovolaemia	Y/N
Electrolyte disturbance (state ....)	Y/N
Anaemia (Hb<10)	Y/N
Malnutrition	Y/N
Marked obesity	Y/N
Septicaemia	Y/N
Diabetes	Y/N
Dementia or confusion	Y/N
Too sick for above to be determined	Y/N
Other (state ....)	Y/N

Hypertension	Y/N
Heart failure	Y/N
Valvular disease	Y/N
IHD	Y/N
Non-sinus ECG	Y/N
Other significant ECG abnormality (state ....)	Y/N
Acute respiratory disease	Y/N
Chronic respiratory disease	Y/N
Raised creatinine or urea	Y/N
Acute renal failure	Y/N

ANAESTHETIC MANAGEMENT

GA/GA + extradural

Invasive monitoring (IABP/CVP/PAWP) Y/N

POSTOPERATIVE MANAGEMENT

Operation performed .... Duration ....

Did the patient spend enough time in recovery?	Y/N
Was the patient sent to ICU?	Y/N
Would you have sent the patient to ICU but ICU full?	Y/N
Do you think the patient will leave hospital alive?	Y/N
Does the surgeon?	Y/N

Figure 2 Questionnaire used in the study.

Class I

No organic, physiological, biochemical or psychiatric disturbance. The pathological process for which the operation is to be performed is localised and does not entail a systemic disturbance

Class II

Mild to moderate systemic disturbance caused either by the condition to be treated surgically or by other pathophysiological processes

Class III

Severe systemic disturbance or disease of whatever cause, even though it may not be possible to define the degree of disability with finality

Class IV

Severe systemic disorders that are already life threatening, not always correctable by operation

Class V

The moribund patient who has little chance of survival but is submitted to operation in desperation.
Most of these patients require operation as a resuscitative measure with little if any anaesthesia

Figure 3 American Society of Anaesthesiology (ASA) classification of physical status (abridged).

After a variable is added to the model, the model is reviewed so that any redundant variables are removed. The modelling process is stopped when there are no more significant explanatory variables. The resulting model can be used to calculate a predicted probability that a particular patient will be in a particular outcome group (equation 1). Significance levels of $P < 0.05$ and $P < 0.1$ were used as indicated.

$$P = e^{\operatorname{logit} p}/(1 + e^{\operatorname{logit} p})$$

Where $\operatorname{logit} p = b_0 + b_1V_1 + b_2V_2 + b_3V_3 + \ldots$, where b_0 is the model intercept, b_1b_2 are the parameter estimates for variables V_1V_2 and P is probability of survival.

Table 1 Patient characteristics (mean (range) or number)

	Survivors	Deaths
n	60	47
Age (yr)	66–92 (78)	65–97 (83)
65–74	20	8
75–84	34	22
85–94	10	15
>95	0	3
Sex (M/F)	32/28	22/25
Time of operation		
08.00–17.59	35	16
18.00–24.00	8	10
00.01–07.59	11	18
Not stated	6	3
Preoperative ASA class		
I	2	0
II	20	4
III	30	10
IV	7	23
V	1	10
Risk score		
0–2	24	3
3–5	30	18
6–8	5	21
>8	1	5
Poor condition	20	30
Sepsis	8	17
Bowel obstruction	19	9
Discussed with consultant surgeon	29	27
Discussed with consultant anaesthetist	34	24
Adequate resuscitation	53 (2 not stated)	30 (2 not stated)

Table 2 Patient management. *ICU full for five patients. **Five patients died in theatre; in nine cases ICU was full. ns=not stated

	Survivors	Deaths
n	60	47
Anaesthetist		
Consultant/senior registrar	35	21
Registrar	11	12
SHO	10	7
Staff grade	4	7
Not stated	0	0
Surgeon		
Consultant/senior registrar	39	20
Registrar	14	22
SHO	3	0
Staff grade	4	4
Not stated	0	1
General extradural and anaesthetic	33	22
Invasive monitoring	18	39
Operation performed		
Bowel resection	15	18
No resection	24	12
AAA	3	5
Not stated	18	12
Duration of operation		
<2 h	31	20
2–3 h	20	15
>3 h	5	11
Not stated	4	1
Transferred to ICU after operation	6*	21**
Correct opinions before operation		
Anaesthetist	52 (3ns)	32 (1ns)
Surgeon	50 (4ns)	18 (2ns)
Correct opinions after operation		
Anaesthetist	52 (0ns)	34 (3ns)
Surgeon	52 (1ns)	28 (2ns)

Results

Data were collected from 107 patients, of whom 47 died. The age range was 65–97 yr. Patient characteristics and univariate analysis data are presented in tables 1–3.

The multiple logistic regression modelling death, when the opinions of the medical staff were not used in the model, had five factors that were significant at $P < 0.05$. The parameter estimates are shown (table 4); a negative parameter estimate increases the estimated probability that the patient will die. For example, women have an increased probability of death (the parameter estimate is −1.57). The estimated probability of death increases with increasing age and increasing ASA class. Admission to the ICU and use of invasive monitoring are also associated with increased mortality.

The area under the receiver operating characteristic curve for this model has an area of 0.93 (SD 0.02) (fig. 4). This suggests that 93% of the variability in mortality is explained by the five explanatory variables in this model.

If the criterion for variable selection is relaxed (to $P < 0.1$) then other variables are included in the model: an SHO anaesthetist decreases the risk of dying ($P = 0.07$) and if the senior surgeon present is a consultant the estimated probability of dying increases. If the opinions about survival recorded by the surgeon and the anaesthetist before and after operation are offered as potential factors, the opinion of the anaesthetist after operation is a significant factor explaining outcome ($P = 0.02$). If only the opinions given before surgery are offered as potential explanators, then neither that of the surgeon nor the anaesthetist is selected as significant at $P < 0.1$.

Six factors were significantly associated with the anaesthetist predicting, before the operation, that the

Table 3 Occurrence of potential explanatory factors by outcome group; *indicates significant difference between outcome groups using univariate statistics

	Survivors (n=60)	Deaths (n=47)
*Evidence of sepsis	8	17
*Admitted to ICU	6	21
*Adequately resuscitated	53	30
*Poor general condition	20	30
Bowel resection	15	18
Bowel obstruction	19	9
Female	28	25
*Invasive monitoring	18	39
General and extradural anaesthesia	33	22

Table 4 Parameter estimates (SE) of factors associated with death, at a selection criterion of P=0.05. Medical staff's opinions were not offered as potential explanators of outcome

Variable	Parameter estimate (SE)	P	Odds ratio
Intercept	21.051 (5.163)	0.0001	
Age	−0.137 (0.049)	0.005	0.87
Female sex	−1.572 (0.740)	0.03	0.21
Invasive monitoring	−1.862 (0.698)	0.008	0.16
ICU admission	−2.429 (0.888)	0.006	0.09
ASA status	−1.750 (0.458)	0.0001	0.17

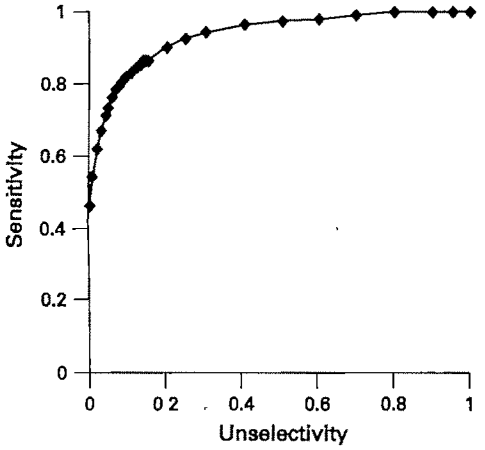

Figure 4 Receiver operating characteristic curve for mortality, described by all variables except opinions. Area under curve = 0.93, SD = 0.02.

patient would die ($P < 0.1$, table 5). The anaesthetist was more likely to predict death in patients with higher ASA class, greater age ($P = 0.06$), poor condition and when the senior surgeon was a registrar. The anaesthetist was less likely to predict death when the patient was adequately resuscitated and when the pathology was bowel obstruction.

Seven factors were significantly associated with the anaesthetist predicting, after the operation, that the patient would die ($P < 0.1$, table 6). In the opinion of the anaesthetist the probability of the patient dying was increased when the patient was in a 'poor condition', had sepsis or had undergone bowel resection. The probability increased with increasing patient age and ASA class. If the anaesthetic technique included extradural anaesthesia in addition to general anaesthesia, or if the anaesthetist was a consultant, the estimated probability decreased. Three factors (ASA status, age and poor condition) were common to the models of anaesthetic opinion both before and after operation.

Table 5 Parameter estimates (SE) of factors associated with the anaesthetist's opinion, before operation, of the likelihood of death, at a selection criterion of P=0.1. Medical staff's opinions were not offered as potential explanators of outcome

Variable	Parameter estimate (SE)	P
Intercept	20.57 (6.92)	0.003
Age	−0.11 (0.06)	0.06
Obstruction	1.93 (0.94)	0.04
Adequate resuscitation	2.22 (1.03)	0.03
Registrar surgeon	−2.52 (0.94)	0.007
Poor condition	−2.12 (1.00)	0.03
ASA status	−3.11 (0.79)	0.0001

Table 6 Parameter estimates (SE) of factors associated with the anaesthetist's opinion after operation of the likelihood of death, at a selection criterion of P=0.1. Medical staff's opinions were not offered as potential explanators of outcome

Variable	Parameter estimate (SE)	P
Intercept	16.15 (4.70)	0.0006
Age	−0.12 (0.05)	0.02
Consultant anaesthetist	1.55 (0.73)	0.03
Poor condition	−2.42 (0.73)	0.001
Sepsis	−2.16 (0.81)	0.008
General anaesthetic and extradural	1.25 (0.76)	0.1
Bowel resection	−2.46 (0 84)	0.003
ASA status	−1.32 (0.43)	0.002

Table 7 Parameter estimates (SE) of factors associated with the use of invasive monitoring. The selection criterion was P=0 1 Medical staff's opinions were not offered as potential explanators of outcome

Variable	Parameter estimate (SE)	P
Intercept	0.4 (0.56)	0.44
Consultant anaesthetist decision	−3.283 (1.18)	0.005
Consultant surgeon	−2.3 (1.32)	0.08
Senior registrar surgeon	1.32 (0.62)	0.03
Consultant anaesthetist	5.06 (1.29)	0.0001
Poor condition	−1.72 (0.63)	0.007
ICU admission	−2.65 (0.87)	0.002

Six factors were significant explanators ($P < 0.1$) of whether or not invasive monitoring was used (table 7). The probability of invasive monitoring being used was reduced if the senior surgeon was a senior registrar or the senior anaesthetist was a consultant. The probability was increased if the senior surgeon was a consultant, the patient was in 'poor condition', if the patient was admitted to ICU after the operation or if a consultant anaesthetist was involved in the decision to operate.

Table 8 illustrates how the model might be used to ascribe a probability of death to individual patients. This is included to illustrate the model, but validation is necessary before such use of the model can be recommended.

Table 8 Predicted survival, calculated from the model, of individual patients with specific characteristics

Age (yr)	ASA status	Sex	Admission to ICU	Invasive monitoring	Predicted probability of survival (%)
65	I	No	No	Yes	100
75	III	Yes	No	No	98
75	IV	Yes	Yes	Yes	10
85	III	Yes	Yes	yes	45

Discussion

Several of the factors recorded before operation are subjective (such as poor condition, adequate resuscitation). These terms were used to allow for individual assessment of factors not detected by lists of pathophysiological factors. This practical approach to detecting factors that may influence overall assessment or treatment of patients is similar to that used by other investigators, and is supported by the findings of the Riyadh Intensive Care group.[9]

We confirmed that patients aged over 65 yr undergoing urgent or emergency surgery have a high risk of dying. We found that 44% of these patients died without leaving hospital. No patient of ASA class IV or V and aged over 85 yr survived. The factors significantly associated with death in this study are consistent with other studies.[10 11] Age and ASA status were factors in models of mortality and of the anaesthetist's opinion, both before and after operation, regarding the chance of survival. Neither factor was a significant explanator of the use of invasive monitoring. Individual risk factors in the anaesthetic assessment, and a risk factor score that summed these factors, did not predict outcome.

Is age itself is a risk factor for surgery? Mortality after surgery undoubtedly increases with age[12] but this could be because of the increased prevalence of medical conditions.[3] We found greater age to be associated with a greater likelihood of death irrespective of co-morbidity.

There has been debate about the predictive ability of the ASA classification since its first description.[13-15] Patients in the higher ASA classes have higher risk of dying,[11] but some argue that ASA status, on its own, cannot usefully discriminate between outcome groups because it does not take operative factors into consideration.[15 16] In the present study all patients had similar major surgery and the ASA status helped predict the likelihood of death, confirming the value of this semi-subjective tool.[15]

We found that women had a greater probability of dying. There are several possible explanations for this: women may have a higher incidence of co-morbidities such as cardiac or respiratory problems; women may present at a later stage of illness and thus be more unwell before they receive treatment; or the diseases that lead to laparotomy may differ in women compared with men. This pilot study cannot differentiate between these possible explanations but it highlights an area for future research. A previous study of surgical gastrointestinal emergencies found that women responded less well to resuscitation efforts than men.[12] Failure to respond to resuscitation was associated with increased mortality and morbidity.

The estimated probability of death was increased in patients who were admitted to the ICU or who had invasive haemodynamic monitoring (no deaths were caused by complications of invasive monitoring). Initially this might seem to be counter-intuitive, but it could reflect appropriate use of both these interventions. Those patients that are most sick are admitted to the ICU and have invasive monitoring started in theatre. This illustrates that although a significant explanator of an outcome, in this case death, does not necessarily influence outcome, it may be a marker of something else that influences the outcome. This is important because our data should not be interpreted as implying that reducing invasive monitoring would improve outcome.

The model of the anaesthetist's opinion, before operation, of the likelihood of survival had only two factors in common with the model of actual mortality: age and ASA status. Of the other significant factors, 'poor condition' and 'adequate resuscitation' might be expected to be selected, because they are subjective terms and are thus likely to correlate well with the anaesthetist's opinion of whether the patient will survive. The grade of surgeon and anaesthetist tends to be similar for any given operation. Thus 'registrar surgeon' as a significant explanator of the anaesthetist's opinion of the likely outcome may reflect anaesthetists' opinion that the patient is more likely to die if the surgeon is a registrar; alternatively the registrar anaesthetists who work with registrar surgeons may be generally more pessimistic about patient survival. The finding that the absence of bowel obstruction is an explanator of anaesthetist's preoperative opinion may represent a belief that patients with bowel perforation or abdominal aneurysm have a higher mortality than patients with obstruction. However we found no significant difference in outcome between these groups with univariate or multivariate analysis.

The model of the anaesthetist's opinion, after operation, of survival had three variables in common with the model before operation (age, ASA status and poor condition). Of the other factors associated with anaesthetic prediction, after operation, of death, two factors were available before operation (presence of sepsis and the absence of a consultant anaesthetist) and two were not (bowel resection and the absence of extradural anaesthesia). The anaesthetist was more likely to believe the patient would survive when extradural anaesthesia was used. This may be because the most sick patients were too unstable or urgent to permit use of extradural anaesthesia or because anaesthetists using extradural anaesthesia believe it reduces risk. If the senior anaesthetist was a consultant then the estimated probability of death decreased. This may be because consultants treated fitter patients than other anaesthetists or consultants may be more optimistic; we could not differentiate between these two possibilities.

Invasive monitoring was a significant explanator of mortality, and we used the model of whether invasive monitoring was undertaken to study this feature. If a consultant anaesthetist was involved in the decision to operate it was more likely that invasive monitoring was used. However, if a consultant anaesthetist was involved in treatment, the use of invasive monitoring was less likely. Consultant anaesthetists asked for their opinion may err on the side of caution and suggest the use of invasive monitoring, but when treating a patient may judge that some patients do not require it. Admission to the ICU was associated with the use of invasive monitoring and this may partly account for the greater use of invasive monitoring when a consultant was involved in the decision to operate. The grade of the senior surgeon also had an effect: invasive monitoring was more likely when the senior surgeon was a consultant and less likely when he or she was a senior registrar.

We have identified several factors that could be used to predict mortality in patients aged over 65 yr undergoing urgent or emergency laparotomy. These factors are easily determined and do not require complex investigation. Before the widespread use of a model using these findings can be recommended the model must be validated to establish that it can be generalized. The factors associated with survival and those associated with the anaesthetist's opinions about survival differ. Greater age and ASA class are explanators of survival in this group of patients and also explanators of anaesthetist's opinions about survival. This implies that anaesthetists correctly include these factors when assessing patient risk. However anaesthetist's opinions are associated with some factors that do not predict outcome and not associated with some that do. As opinions about survival are likely to influence postoperative management of these high-risk patients, further development of an objective tool to determine risk might be useful. The goal of applying such a model to individual patients remains a long way off.

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LABORATORY INVESTIGATIONS

Hepatic energy metabolism during ketamine and isoflurane anaesthesia in haemorrhagic shock

K. TAKAHASHI, S. NOSAKA, S. MORIKAWA, T. INUBUSHI

Summary

The effects of ketamine and isoflurane on the phosphoenergetic state of the liver during haemorrhage were investigated using ^{31}P nuclear magnetic resonance (NMR) spectroscopy. Male Wistar rats were anaesthetized with ketamine (1.0 mg kg^{-1} min^{-1} i.v., Ket 1.0 group, or 1.5 mg kg^{-1} min^{-1} i.v., Ket 1.5 group), or isoflurane 1.4% (Iso group). Haemorrhage was induced by withdrawing blood until the mean arterial pressure was reduced to 40 mm Hg, and this pressure level was then maintained for 45 min. Hepatic energy metabolism was evaluated from the changes in adenosine triphosphate (ATP) and inorganic phosphate (Pi). The β-ATP decrease and the Pi increase were more marked in the two Ket groups than in the Iso group. At 20 min after haemorrhage, the β-ATP peak areas were 34%, 32% and 76%, and the Pi peak areas were 257%, 260% and 160% of their initial values in the Ket 1.0, Ket 1.5 and Iso groups, respectively. NMR data were supported by chemical assessments. These results demonstrated that, in terms of phosphoenergetic levels, a continuous administration of 1.0 or 1.5 mg kg^{-1} min^{-1} ketamine markedly decreased hepatic metabolism during haemorrhagic shock, whereas inhalation of 1.4% isoflurane mitigates the metabolic damage. (*Br. J. Anaesth.* 1998; **80**: 782–787)

Keywords: anaesthetics i.v. ketamine; anaesthetics volatile isoflurane; haemorrhage; metabolism energy expenditure hepatic; nuclear magnetic resonance spectroscopy

General anaesthetics influence haemodynamic systems and cause changes in cardiac output and peripheral vascular resistance. Inhalation anaesthetics reduce blood pressure and depress spontaneous respiration, as do almost all i.v. anaesthetics, including barbiturates and propofol.[1] Therefore, for induction of anaesthesia in shock patients, the choice of anaesthetics requires careful consideration. In such cases, ketamine is thought to be advantageous because of its effect of maintaining cardiopulmonary stability,[2] although ketamine was observed to have negative inotropic effects on the myocardium *in vitro*.[3] Ketamine has been used as one of the anaesthetic agents in total i.v. anaesthesia, combined with droperidol, propofol and fentanyl, for many types of surgery.[4] Under normovolaemic conditions, ketamine has been reported to increase cardiac output and to maintain tissue perfusion, including that of the liver, in dogs[5] and rats.[6] However, some investigators have demonstrated a decrease in cardiac output with ketamine anaesthesia in rats.[7] Of the inhalation anaesthetics, it is well known that isoflurane increases the hepatic blood flow and is more effective at maintaining hepatic oxygen supply than halothane and enflurane in rats.[8–10] However, in critical situations, such as massive haemorrhage and hypotension, the effects of anaesthetics might be changed. Seyde and Longnecker[11] demonstrated that the total hepatic blood flow, especially in the hepatic artery, decreased markedly in rats receiving ketamine compared with those receiving isoflurane after haemorrhage. This finding suggests that the effects of ketamine on the hepatic circulation in shocked patients, such as those who have experienced haemorrhage, differ from those under normovolaemic conditions. The balance between hepatic oxygen supply through hepatic blood flow and oxygen consumption by hepatocytes is an essential factor in hepatic metabolism.[12] The reduction of hepatic blood flow may impair hepatic energy metabolism. In our previous study,[13] isoflurane reduced impairment of the phosphoenergetic state in rat liver during haemorrhagic shock compared with halothane. However, the influence of ketamine on hepatic metabolism during haemorrhage has not been examined. *In vivo* ^{31}P nuclear magnetic resonance (NMR) spectroscopy provides non-invasive, real-time information on phosphoenergetics.[14] In the present study, the effects of ketamine on the phosphoenergetic state of the rat liver during haemorrhagic shock were evaluated by *in vivo* ^{31}P NMR spectroscopy and compared with those of isoflurane.

Methods

ANIMAL PREPARATION

The experimental protocol was approved by the Animal Investigation Committee of Shiga University of Medical Science. Sixty male Wistar rats, weighing 300–350 g, were given free access to rat chow and

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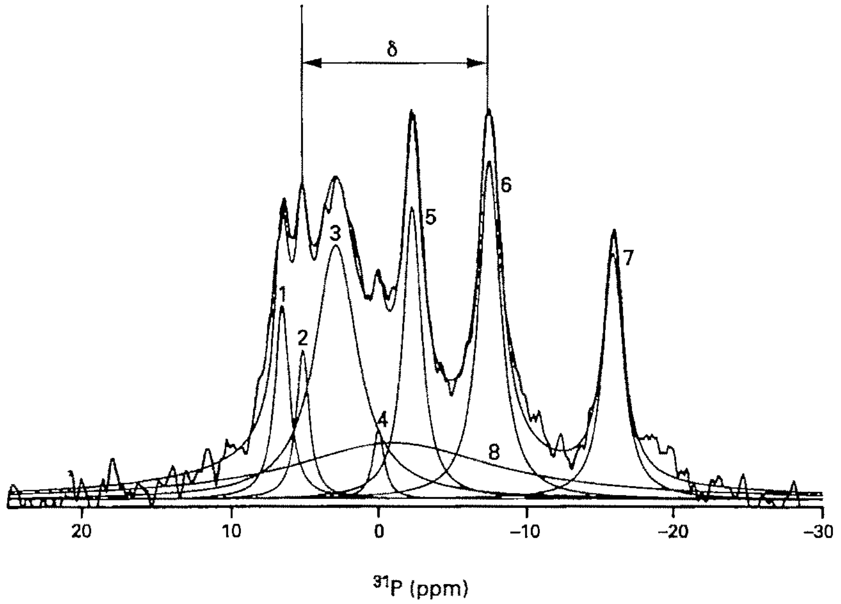

Figure 1 Analysis of the *in vivo* ^{31}P NMR spectrum of the rat liver. Peak identification: 1 = phosphomonoester; 2 = inorganic phosphate (Pi); 3 = phosphodiester; 4 = phosphocreatine (PCr); 5 = γ-P of adenosine triphosphate (γ-ATP); 6 = α-ATP; 7 = β-ATP; 8 = baseline; δ represents the chemical shift between Pi and α-ATP peaks.

water *ad libitum*. The rats were randomly divided into three groups, Ket 1.0, Ket 1.5 and Iso. Ket 1.0 and 1.5 group rats were given 50 mg kg^{-1} of ketamine intraperitoneally, and thereafter the left femoral vein and artery and left carotid artery were cannulated with polyethylene tubes Rats inhaled 100% oxygen during surgery. Iso group animals inhaled twice the minimum alveolar concentration (MAC) of isoflurane (2.8%)[15] carried in 100% oxygen, and the same cannulations were performed. Following vascular access, a tracheostomy was performed in each animal and ventilation was mechanically controlled with 100% oxygen using an animal ventilator (model SN-480-7, Shinano, Tokyo, Japan). Pancuronium bromide (0.1 mg kg^{-1}) was given intravenously. In the Ket 1.0 and Ket 1.5 groups, 1.0 mg kg^{-1} min^{-1} and 1.5 mg kg^{-1} min^{-1} of ketamine in saline (4.0 ml kg^{-1} h^{-1}) respectively was infused intravenously throughout the experiment. In the Iso group, following tracheostomy, the concentration of isoflurane was reduced to 1 MAC (1.4%), and 4.0 ml kg^{-1} h^{-1} of saline was infused continuously. Arterial blood pressure was monitored using a transducer (TRANSPAC VI, Abbott Critical Care Systems, Sligo, Eire) and body temperature maintained at 36–37°C, with a heating pad monitoring the intrarectal temperature. Rats were laparotomized with a transverse incision.

NMR MEASUREMENT

A 2-tesla CSI Omega System (Bruker, Fremont, CA, USA) was used for the NMR measurement. A custom-made 18-mm diameter surface coil was placed between the left lateral and median lobes of the liver. The probe was dually tuned to ^1H (85.6 MHz) and ^{31}P (34.6 MHz) frequencies and sealed with silicone rubber. The rat was placed on an acrylic cradle at the centre of the magnet. The magnetic field homogeneity was optimized with a water ^1H signal. ^{31}P NMR data were collected using a single pulse sequence with a 70° pulse at the coil centre. The acquisition parameters were as follows: 512 data points, spectral width 3000 Hz, repetition time 400 ms, and 740 acquisitions. Acquisition time for one data set was 5 min.

EXPERIMENTAL PROCEDURE

Under normotensive conditions, two control data sets were collected. In 18 rats (six for each group),

Table 1 Mean arterial blood pressure, arterial blood gas analysis, body temperature before and after shock, and haemorrhaged blood volume. Values are means (SD); *n* = 6 in each group. MAP = mean arterial blood pressure, Pa_{CO_2} = arterial carbon dioxide partial pressure, Pa_{O_2} = arterial oxygen partial pressure, HCO_3 = bicarbonate concentration, HV = haemorrhaged volume. *Significantly different from the two Ket groups

	Before shock			After shock		
	Ket 1.0 (ketamine 1.0 mg kg^{-1} min^{-1})	Ket 1.5 (ketamine 1.5 mg kg^{-1} min^{-1})	Iso (isoflurane 1.4%)	Ket 1.0 (ketamine 1.0 mg kg^{-1} min^{-1})	Ket 1.5 (ketamine 1.5 mg kg^{-1} min^{-1})	Iso (isoflurane 1.4%)
MAP (mm Hg)	109.2 (8.61)	114.2 (7.36)	110.9 (8.00)	40	40	40
pH	7.37 (0 05)	7.35 (0.02)	7.38 (0.05)	7.15 (0.05)	7.18 (0.06)	7 22 (0.03)
Pa_{CO_2} (mm Hg)	34 2 (3.78)	31.7 (2.89)	32.7 (5.48)	33 6 (1.89)	29.6 (3.08)	33.1 (2.95)
Pa_{O_2} (mm Hg)	307.4 (28.5)	310.8 (27.7)	307.3 (27.0)	315.4 (20.2)	316.0 (51.3)	333.1 (38 8)
HCO_3 (mmol l^{-1})	21 8 (0.94)	22.0 (1.31)	21.2 (0.82)	13.1 (2.29)	11 8 (1.65)	13.0 (0.51)
Base excess	1.07 (2.29)	−2.53 (0.92)	−3.08 (0.94)	−11.9 (1.67)	−15.2 (2 53)	−13.6 (2.12)
Body temperature (°C)	36 9 (0.25)	36.8 (0.49)	36.7 (0.37)	36.7 (0.37)	36.4 (0.19)	36.3 (0.29)
HV (mk kg^{-1})				15 6 (0.91)	15.9 (1.93)	21.3 (1.11)*

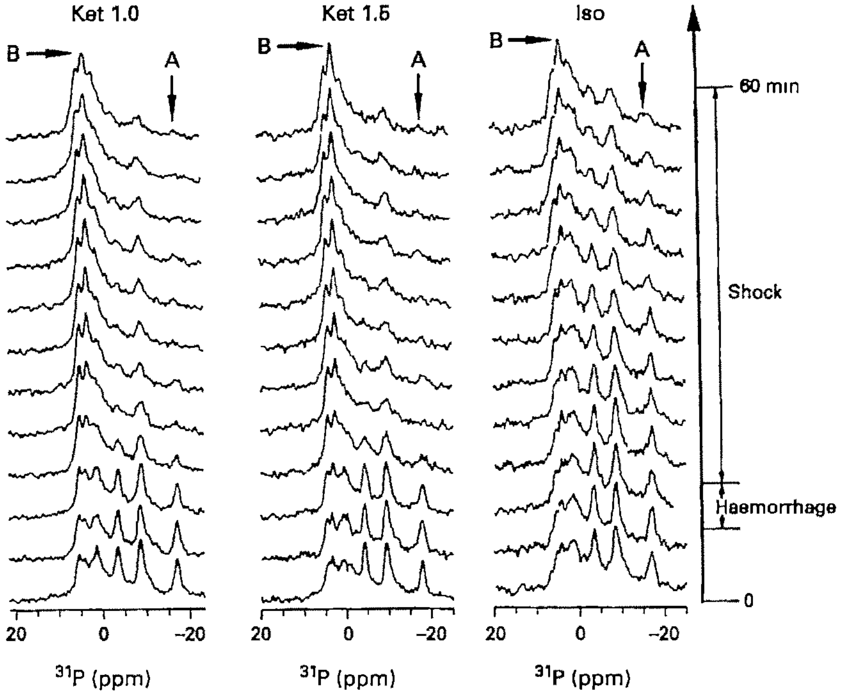

Figure 2—Sequential series of ^{31}P NMR spectra of the liver in three groups of anaesthetized rats. (A) β-adenosine triphosphate, (B) inorganic phosphate. Group Ket 1.0 received ketamine 1.0 mg kg^{-1} min^{-1} i.v., group Ket 1.5 ketamine 1.5 mg kg^{-1} min^{-1} i.v., and group Iso isoflurane 1.4%.

blood was rapidly withdrawn through the carotid artery into a reservoir for at least 5 min, until the mean arterial pressure (MAP) was reduced to 40 mm Hg. Additional blood was removed as needed to maintain this low blood pressure. The hypotensive period was maintained for 45 min. NMR data were sequentially collected throughout the experiment, and 12 total NMR data sets were acquired. At the end of the experiment, the shed blood volume was measured. The volume of arterial blood gas samples was excluded. In 12 rats (four for each group) prepared in the same manner, NMR measurements were carried out without haemorrhage, to act as a control experiment. Arterial blood gas analysis was performed with a CIBA-CORNING 280 Blood Gas System (Ciba Corning Diagnosis Co., Medfield, MA, USA) before and at the end of the experiment.

DATA ANALYSIS

Data obtained were Fourier-transformed with 10 Hz line broadening. The spectral data were analysed using an automatic curve fitting process using a Simplex procedure.[16] The peaks were broken down into eight components of Lorentzian line shapes: phosphomonoester, inorganic phosphate (Pi), phosphodiester, phosphocreatine (PCr), γ-P of adenosine triphosphate (γ-ATP), α-ATP, β-ATP, and a baseline, as shown in fig.1. The PCr peak results from abdominal muscle signal contamination. The intracellular pH (pHi) was calculated from the difference (δ) between the Pi and α-ATP chemical shifts according to the following equation[17]:

$$\text{pHi} = 6.75 + \log ((\delta - 10.85) / (13.25 - \delta))$$

CHEMICAL ANALYSES

Chemical analyses were carried out using another 30 rats prepared in the same manner as that used for the NMR measurement. The liver was freeze-clamped before (n = for each group) and 20 min after haemorrhage (n = 5 for each group) with Wallenburger tongues pre-cooled in liquid nitrogen. The frozen liver was ground and weighed, and the metabolites were extracted by four volumes of 6% perchloric acid. After neutralization with KOH, the supernatant was stored at −80°C until analysis. The contents of ATP, adenosine diphosphate and adenosine monophosphate were determined using a

Table 2 Chemical determination of phosphate compounds in the liver extract. Values are means (SD); n = 5 in each phase in each group. ATP = adenosine triphosphate, ΣAd = total adenine nucleotides, EC = energy charge: (ATP + 1/2ADP) / (ATP + ADP + AMP), Pi = inorganic phosphate. The content of ATP, Σ Ad and Pi is expressed in μmol g^{-1} wet weight of liver. *Significantly different from the two Ket groups

	Before shock			After shock		
	Ket 1.0 (ketamine 1.0 mg kg^{-1} min^{-1})	Ket 1.5 (ketamine 1.5 mg kg^{-1} min^{-1})	Iso (isoflurane 1.4%)	Ket 1.0 (ketamine 1.0 mg kg^{-1} min^{-1})	Ket 1.5 (ketamine 1.5 mg kg^{-1} min^{-1})	Iso (isoflurane 1.4%)
ATP	3.09 (0.38)	2.95 (0.38)	2.95 (0.46)	0.94 (0.23)	0.80 (0.36)	1.83 (0.33)*
Pi	2.50 (0.41)	2.61 (0.68)	2.33 (0.39)	4.02 (0.49)	4.19 (0.54)	3.18 (0.79)
ATP/Pi	1.28 (0.34)	1.18 (0.28)	1.28 (0.22)	0.24 (0.08)	0.19 (0.08)	0.61 (0.22)*
Σ Ad	4.25 (0.47)	3.91 (0.54)	3.95 (0.70)	2.60 (0.27)	2.45 (0.51)	3.21 (0.21)*
EC	0.84 (0.02)	0.86 (0.01)	0.85 (0.02)	0.52 (0.08)	0.51 (0.09)	0.73 (0.05)*

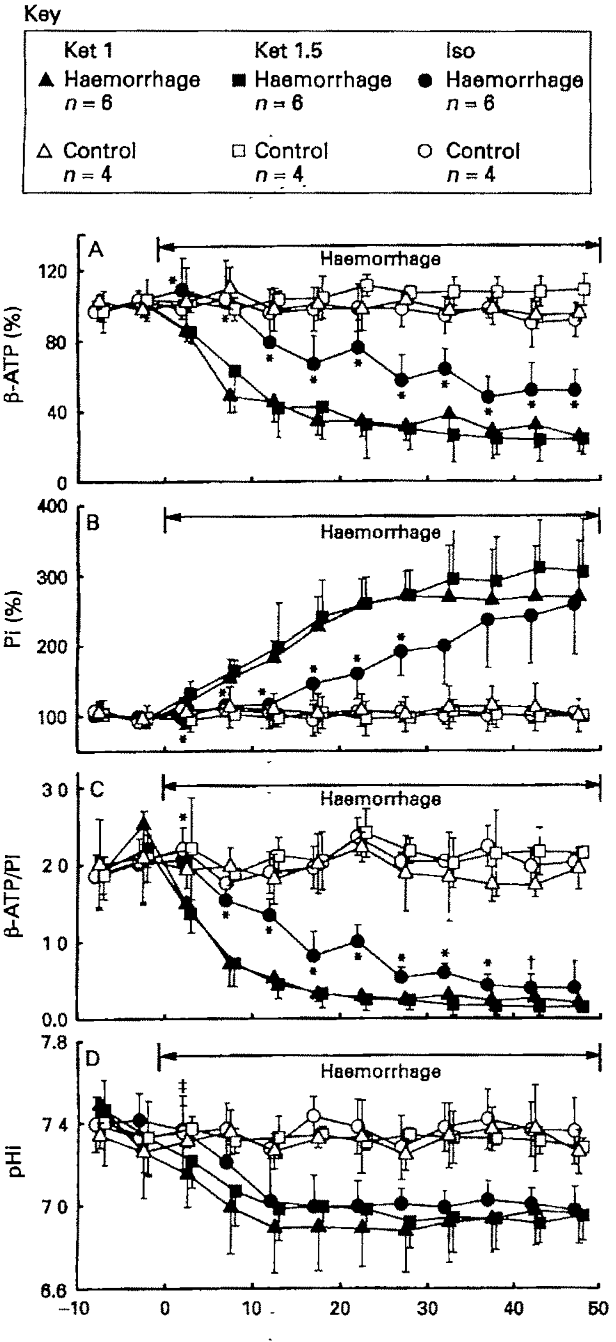

Figure 3 Serial changes in (A) β-adenosine triphosphate, (B) inorganic phosphate (C) β-adenosine triphosphate/inorganic phosphate ratio, and (D) intracellular pH. Peak areas in (A) and (B) are shown as ratios to the corresponding peaks in the first two spectra. Values are mean (SD). *Significantly different from the two Ket groups, †from the Ket 1.5 group and ‡from the Ket 1.0 group (fig. 2).

high-performance liquid chromatography (HPLC) with an isocratic ion-pair reversed-phase assay (Cosmosil $5C_{18}$ 4.6 × 150 mm plus $5C_8$ 4.6 × 150 mm; Nacalai Tesque, Kyoto, Japan) according to the method described by Sellevold and colleagues.[18] The content of Pi was determined essentially by the procedure of Fiske and Subbarow.[19]

STATISTICAL ANALYSIS

The data are expressed as mean (SD). NMR data at individual time points, arterial blood gas analysis data, haemorrhaged blood volume and the values of chemical analyses among the three groups were analysed with one-way analysis of variance. When a significant difference was found, multiple comparisons were conducted by the Student–Newman–Keuls test. $P < 0.05$ was considered significant.

Results

As summarized in table 1, no significant differences between the three groups were detected in MAP, arterial blood gas analysis and body temperature before and after haemorrhage. However, the blood volume to induce haemorrhagic shock in the Iso group was significantly larger than that in the two Ket groups, although those in the two Ket groups were not different. All data without haemorrhage in either group were constant, and no significant difference was observed among the three groups (data not shown).

Figure 2 shows representative series of ^{31}P NMR spectra in the Ket 1.0, Ket 1.5 and Iso groups. During haemorrhage, the β-ATP peaks decreased and the Pi peaks increased markedly in all groups. The changes in the β-ATP and Pi peak areas relative to the corresponding peaks in the first two spectra are shown in figs 3(A) and 3(B). The decrease in β-ATP and the increase in Pi were more marked in the two Ket groups than in the Iso group, especially during the early phase of haemorrhage. Twenty min after the haemorrhage, the β-ATP peak areas were 34%, 32% and 76%, and the Pi peak areas were 257%, 260% and 160% of their initial values in the Ket 1.0, Ket 1.5 and Iso groups respectively. The β-ATP/Pi ratio was calculated as a parameter to evaluate the hepatic energy level. During haemorrhage, the β-ATP/Pi ratio was reduced in all groups, as shown in fig. 3(C). The β-ATP/Pi ratios in the two Ket groups were significantly lower than those in the Iso group. The changes in pHi are shown in fig. 3(D). No significant difference in pHi among the three groups was detected even during the shock period. There was no significant difference between the Ket 1.0 and Ket 1.5 groups throughout the experiment in any parameter. In controls (without haemorrhage), all of these values remained constant throughout the experiment in all groups, and no significant difference was observed among the three groups.

The contents of ATP and Pi, the ATP/Pi ratio and the energy charge determined by chemical analyses before and at 20 min after haemorrhage are summarized in table 2. Before haemorrhage, no significant difference was detected among the three groups. At 20 min after haemorrhage, the contents of ATP decreased to 30%, 27% and 64%, and the contents of Pi increased to 161%, 160% and 136% of their initial values in the Ket 1.0, Ket 1.5 and Iso groups respectively. The contents of ATP in the two Ket groups were significantly lower than that in the Iso group in the shocked condition. The contents of Pi in the Ket groups increased markedly compared with the Iso group; however, no significant difference was observed among the three groups. The ratios of ATP/Pi in the Ket groups were clearly lower than that in the Iso group. In addition, the total adenine nucleotides and energy charge values, which could not be obtained by ^{31}P NMR, were significantly lower in the two Ket groups. No significant difference in either parameter was detected between the two Ket groups.

Discussion

For comparisons of i.v. with inhaled anaesthetics, the depth of anaesthesia is an essential problem. Seyde and colleagues[11] carried out a comparative study of anaesthetics in rats with 1.0 mg kg^{-1} min^{-1} of ketamine and 1 MAC of isoflurane (1.4%). Idvall and colleagues used 1.5 mg kg^{-1} min^{-1} of ketamine for a haemodynamic study of rats under normovolaemic[6] and hypovolaemic[20] conditions. In the present study, two different doses of of ketamine (1.0 mg kg^{-1} min^{-1} and 1.5 mg kg^{-1} min^{-1}) were used for comparison with 1.4% isoflurane to bracket the difference in the depth of anaesthesia achieved with each agent. Without haemorrhage, the MAPs, arterial blood gas parameters, β-ATP and Pi peaks with NMR spectroscopy, and metabolite concentrations determined by the chemical assay were constant throughout the experiment, and no significant difference was detected among the three groups. In addition, the arterial blood gas analysis data after haemorrhage were not different among the three groups. These results suggested that blood oxygenation did not play an important role in the hepatic phosphoenergetic levels of these three experimental groups. Among these measurements, only the blood volume required to induce haemorrhagic shock to MAP 40 mm Hg was significantly lower in the two Ket groups than in the Iso group. In the present investigation, haemorrhagic shock was accomplished by withdrawing blood to keep a fixed mean arterial blood pressure. It has been reported that the normal blood volume of rats is about 7.0 ml $100g^{-1}$.[20 21] Therefore, the haemorrhaged blood volumes in the Ket 1.0, Ket 1.5 and Iso groups correspond to 22.3%, 22.7% and 30.4% respectively of the total blood volume. This result indicates that the effects of ketamine and isoflurane on the cardiovascular system were different during haemorrhagic shock. Rats anaesthetized with two doses of ketamine were less tolerant of the acute bleeding than those anaesthetized with 1.4% isoflurane.

Previously, hepatic and myocardial energy metabolism has been evaluated mainly by biochemical analyses.[8 22 23] *In vivo* ^{31}P NMR spectroscopy has enabled continuous observation of these changes in a living subject. As shown in fig. 3 (A–C), the serial changes in the phosphoenergetic states during haemorrhagic shock were clearly demonstrated in a non-invasive manner. In the two Ket groups, β-ATP decreased and Pi increased more rapidly and extensively; as a result, the β-ATP/Pi, which represents the phosphoenergetic state, decreased more markedly than in the Iso group. No differences in these three parameters were detected between the two Ket groups. These changes indicate the detrimental effect of the continuous administration of ketamine, at either 1.0 or 1.5 mg kg^{-1} min^{-1}, on the liver after haemorrhage when compared with 1.4% isoflurane. The pHi can also be obtained by ^{31}P NMR spectroscopy. No obvious difference in pHi was found among the three groups, although the pHi of the liver in rats anaesthetized with halothane was significantly lower than that of rats anaesthetized with isoflurane during haemorrhagic shock in our previous study.

To assess the NMR data, chemical analyses of phosphorus metabolites were performed before and at 20 min after haemorrhage using tissue extracts, because the difference in the β-ATP/Pi ratios determined by the ^{31}P NMR spectroscopic study was marked at 20 min. As shown in table 2, the contents of ATP and Pi before haemorrhage were not different among the three groups. The chemical determination of ATP, Pi and their ratio at 20 min after haemorrhage supported the relative relationship between them among the three experimental groups indicated by the NMR spectroscopic study. In addition, the energy charge and the total adenine nucleotide levels, which were not obtained by NMR spectroscopy, were reported. Chemical assay measurements also demonstrated a more severe impairment of phosphoenergetics in the two Ket groups compared with the Iso group. The changes in the ATP contents were identical between the two analytical methods. However, the relative increases in Pi during haemorrhage determined by the chemical assay were smaller than those using NMR spectroscopy. The absolute values of the ATP/Pi ratio by chemical analysis were approximately half of those obtained by NMR measurement. It has been suggested that there are two compartments, these being NMR-visible and NMR-invisible. Cunningham and colleagues[24] have reported that the NMR-visible Pi represents 50% of the total Pi in rat liver. This may explain the discrepancy in the ATP/Pi ratios between the two methods. As the Pi newly formed during haemorrhage could be contained mainly in the NMR-visible compartment, the relative changes in Pi determined by the chemical analysis might be smaller than those using NMR measurement.

In conclusion, rats that received 1.0 mg kg^{-1} min^{-1} or 1.5 mg kg^{-1} min^{-1} ketamine showed more severe damage to the phosphoenergetic level in the liver than did rats that received 1.4% isoflurane during haemorrhage, while the phosphoenergetic states were maintained at the same level in the three experimental groups under normovolaemic conditions. Although it is not appropriate to directly apply these data to humans, the continuous administration of ketamine to patients during acute hypovolaemic shock might be undesirable in light of its detrimental effects on hepatic energy metabolism, unlike isoflurane inhalation.

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Possible involvement of multiple human cytochrome P450 isoforms in the liver metabolism of propofol

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Summary

Previous studies of propofol (2,6-diisopropylphenol) pharmacology have shown that this widely used anaesthetic drug is extensively cleared from the body by conjugation of the parent molecule or its quinol metabolite. On the basis of potential influence of propofol on the metabolism of co-administered agents, many investigators have evaluated the effects of propofol on cytochrome P450 (CYP) activities. CYP isoforms involved in propofol metabolism are not defined. In this study, our objective was to elucidate further the CYP isoforms responsible for the hydroxylation of propofol. Using microsomes from 12 different human livers, we investigated CYP isoforms involved in propofol hydroxylase activity, using selective chemical inhibitors of CYP isoforms, correlation with immunoquantified specific CYP isoform content, immunoinhibition, and 11 functionally active human CYP isoforms expressed in a heterologous system (yeast and human B- lymphoblastoid cells). We found a low variability in the production of the hydroxylated metabolite of propofol, 2,6-diisopropyl-1,4-quinol. This activity was mediated by CYP and followed Michaelis–Menten kinetics with apparent K_M and V_{max} values of 18 μM (95% CI 15.1–20.1) and 2.6 nmol min^{-1} mg^{-1} (95% CI 2.45–2.68) respectively. Part of the propofol hydroxylase activity was mediated by CYP2C9 in human liver, especially at low substrate concentration. Moreover, propofol was likely to be metabolized by additional isoforms such as CYP2A6, 2C8, 2C18, 2C19 and 1A2, especially when substrate concentrations are high. This low specificity among CYP isoforms may contribute to the low interindividual variability (two-fold) and may contribute to the low level of metabolic drug interactions observed with propofol. (*Br. J. Anaesth.* 1998; **80**: 788–795)

Keywords: anaesthetics i.v. propofol; cytochrome P450; CYP2C9; interactions (drug)

Propofol (2,6-diisopropylphenol) is one of a series of substituted phenols with highly lipophilic properties resulting in a wide distribution.[1] Propofol is used for its short-lasting anaesthetic action, which results from rapid decay of its plasma concentrations.[1,2] In humans propofol is eliminated from the body only after being metabolized, because less than 0.3% of the dose is excreted from the body as the parent compound and most of the drug (73%) is eliminated as water-soluble conjugates via the kidneys on the first day.[1,3,4] In human beings, the major metabolite is the glucuronic acid conjugate of propofol, which accounts for 53–73% of the total metabolites, depending principally on the administered dose of propofol.[1,4] The importance of this metabolic pathway is also species-dependent.[3,5] The other metabolites recovered in human urine are the two glucuronic acid (conjugation at the C1 or C4 position) and the sulphate conjugates (conjugation at the C4 position) of the ring-hydroxylated derivative of propofol, 2,6-diisopropyl-1,4-quinol (1,4-quinol).[1,4] These minor metabolites need a preliminary hydroxylation at the C4 position. Consequently, hydroxylation of the parent compound accounts for a maximum of 47% of the total dose of propofol.[1,4] All these metabolic pathways reduce or suppress the activity of propofol. Glucuronidation at the 1 or 4 position or sulphation at the 4 position suppress the activity of the compound while the 1,4-quinol has about one-third the hypnotic activity of propofol.[3] This important metabolic clearance to pharmacologically inactive derivatives, associated with a rapid initial distribution phase, limit the effect of propofol and contribute to the excellent recovery from anaesthesia observed in patients.[6]

The total body clearance of propofol is rapid, and as propofol is eliminated only by metabolism, the liver would be expected to be the organ predominantly responsible for the clearance of propofol,[7,8] even if extrahepatic sites such as the kidneys[8] or lungs[9,10] are also involved in propofol glucuronidation.

Previous investigations have shown that propofol decreased animal[11] or human[12] cytochrome P450 (CYP) activities *in vitro*. It has been shown that propofol interacts with the haem moiety of the haemoprotein in the CYP enzyme.[13] The variable inhibition observed in CYP-mediated activities may be attributable to the differential binding of propofol to CYP isoforms.[13] Even if hydroxylation of propofol on its phenol ring is not the major metabolic pathway,[1,4,14] the involvement of the CYP-dependent mono-

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oxygenases in this biotransformation could be the basis of metabolic interactions,[12 15] or of a genetic polymorphism that could explain the particular metabolic profile observed in a patient who exhibited a high conjugation pathway of propofol and a slight ring-hydroxylation.[4] The purpose of the present study was to characterize the isoform(s) of CYP metabolizing propofol. Identification of the major CYP isoform responsible for propofol hydroxylation in humans may aid a better understanding of the inhibitory effects of propofol on CYP-mediated activities.

Materials and methods

DRUGS AND CHEMICALS

Propofol and 2,6-diisopropyl-1-4 quinol were obtained from Zeneca Pharma (Cergy, France). Midazolam was supplied by Roche (Neuilly sur Seine, France). Coumarin, sulphaphenazole, quinidine, diethyldithiocarbamate, troleandomycin, 7-8 benzoflavone, glucose-6-phosphate (G6P), glucose-6-phosphate dehydrogenase (G6PDH), and nicotinamide adenine dinucleotide phosphate ($NADP^+$) were purchased from Sigma (St Quentin Fallavier, France). All sodium dodecyl sulphate-polyacrylamide gel electrophoresis reagents were obtained from Bio-Rad (Paris, France). Other chemicals were of the highest grade commercially available.

HUMAN LIVER MICROSOMES

Experiments with human tissue were approved by the local ethics committee. Fresh human liver samples were obtained from Caucasian patients who underwent partial hepatectomy. Morphologically normal fragments were collected on the material removed in excess and were prepared as reported previously.[16] Less than 10 min elapsed from removal of liver to collecting and freezing a sample in liquid nitrogen. Patients with acute or chronic hepatitis and with cirrhosis were excluded from the study. In correlation studies, 12 different human liver samples (HL1 to HL12) were used.

PREPARATION OF MICROSOMAL FRACTIONS

Microsomes from human livers were prepared by differential centrifugation as described previously.[17] Microsomal fractions were aliquoted in small volumes and stored at −80°C in potassium phosphate buffer (200 mM, pH 7.4) containing 1mM EDTA and glycerol (20%, v/v) before use.

Total CYP content was measured using the method developed by Omura and Sato.[18] Microsomal proteins were assessed according to a modification of Lowry's method using bovine serum albumin as standard.[19]

DETERMINATIONS OF ENZYMATIC ACTIVITIES

Reaction rates were verified to be linear as a function of incubation time and protein concentrations under the conditions described below. In a final volume of 1 ml, a typical reaction mixture contained phosphate buffer (100 mM, pH 7.4 or Tris-HCl buffer 50 mM pH 7.4 for incubations performed with microsomes from human lymphoblastoïd cells) containing an NADPH-generating system composed of $NADP^+$ (0.5 mM), G6P (5 mM), and G6PDH (1.6 unit), 0.5–0.7 mg of microsomal protein, and 10–50 µM propofol. The substrate was prepared daily in methanol and diluted in water (1:100, v/v) before being introduced into the reaction mixture (0.02% methanol final concentration). Reactions were performed at 37°C for 7–10 min; they were started by adding substrate and stopped by adding 50 µl sodium hydroxide (1 mol l^{-1}). Total propofol metabolism by liver microsomes was determined as the amount of 2,6-diisopropyl-1,4-quinol produced (1,4-quinol). Propofol and 2,6-diisopropyl-1,4-quinone (transformed under alkaline conditions from 1,4-quinol) in incubation mixtures were determined by using a gas chromatography-mass spectrometry assay used in our laboratory.[20] Briefly, propofol, its metabolite, and thymol used as an internal standard were extracted in chloroform/ethyl acetate (70:30, v/v). After centrifugation, 1 of the organic layer was injected into the capillary column (HP5: 30 m x 0.25 mm i.d. x 0.25 m film thickness). Propofol, 2,6-diisopropyl-1,4-quinone and thymol were detected by selected ion monitoring at mass/charge ratios of 163 (propofol), 149 (2,6-diisopropyl-1,4-quinone) and 135 (thymol). Identification of the metabolite, 1,4-quinol, was based on co-elution and comparison of the mass spectrum with the authentic standard. Precision and accuracy were below 10% (within-run) and below 16% (between-run) at low concentrations. The limit of detection of 1,4-quinol was 25 ng ml^{-1}.

Coumarin 7-hydroxylase and 7 ethoxycoumarin O-deethylase activities at a substrate concentration of 100 µM were determined fluorometrically as described by Aitio and colleagues.[21] Tolbutamide hydroxylase activity was determined on four different human microsomes. Microsomal incubations with 1 mM tolbutamide (methanol) and 2 mg protein were assessed in a final volume of 1 ml for 1 h at 37°C. Extraction and quantification of hydroxytolbutamide were assayed according to Relling and colleagues with minor modifications.[22]

The effect of substrate concentration on the rate of production of 1,4-quinol was evaluated with a concentration of propofol from 2 µM to 200 µM from three different microsomal fractions. All assays were performed in duplicate or triplicate.

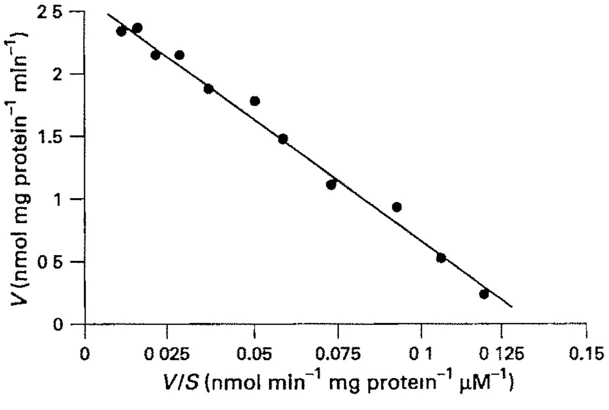

Figure 1 Eadie–Hofstee plot for the formation of the metabolite 2,6-diisopropyl-1,4-quinol after incubation of microsomes from human liver sample HL3. Values are the mean of three separate determinations.

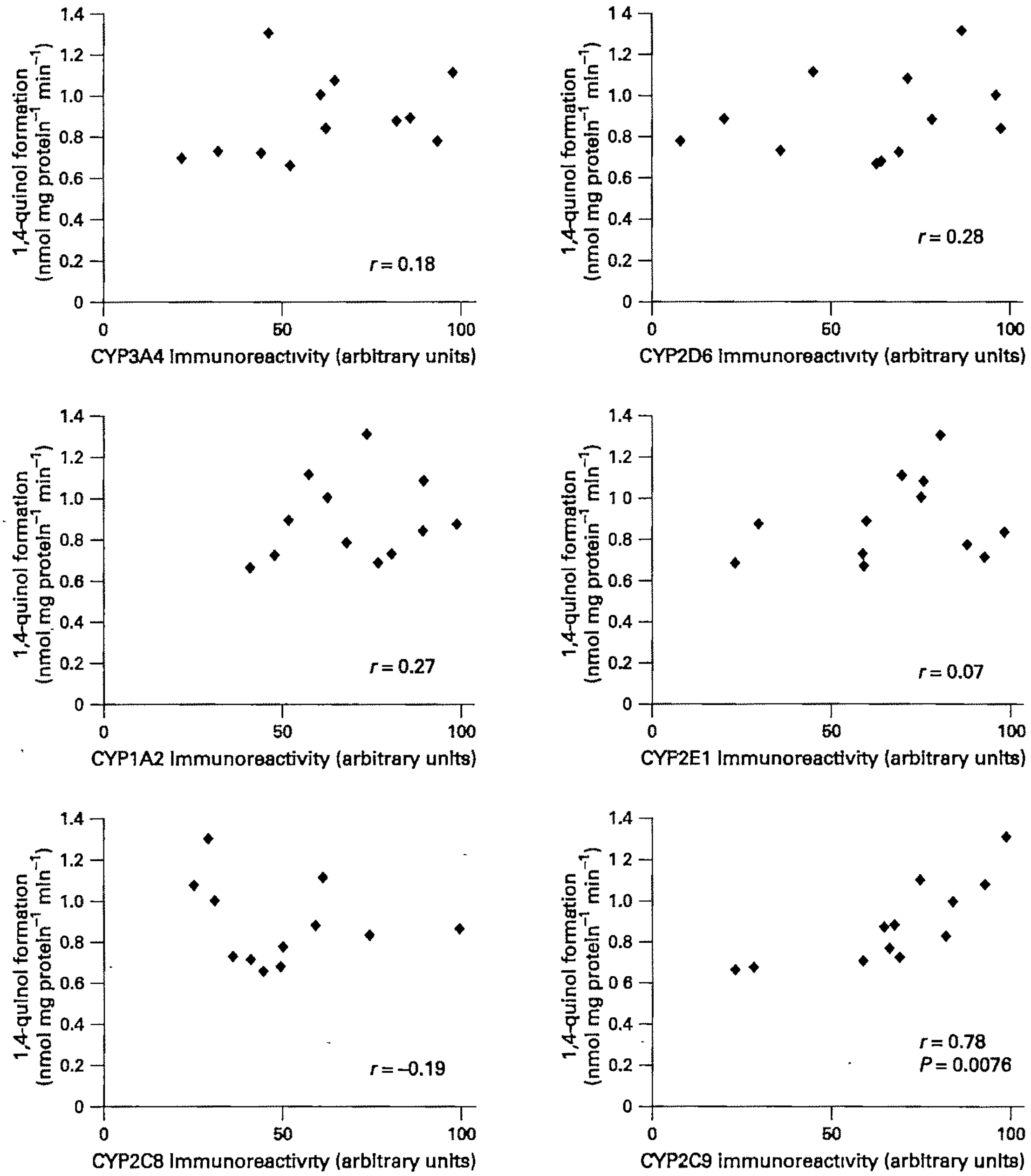

Figure 2 Relationships between microsomal CYP3A4, CYP2D6, CYP1A2, CYP2E1, CYP2C8, CYP2C9 immunoreactive content and the rate of formation of 2,6-diisopropyl-1,4-quinol by 12 different human liver microsome preparations. Each data point represents the mean of triplicate determinations from each human liver and is expressed in arbitrary units (percent of the fraction expressing the highest immunoreactivity). Statistical analysis was performed using a stepwise multiple regression.

INHIBITION STUDY

Effective chemical inhibitors were used as probes of specific CYP isoforms involved in the metabolism of propofol. Inhibitors were introduced into the incubation medium simultaneously with the substrate except for troleandomycin and orphenadrine; these were preincubated with microsomes and the NADPH-generating system at 37°C for 20 min to produce sufficient reactive metabolites, which led to specific inhibition. The reaction was then continued with substrate for an additional 10 min. Inhibitors used as probes of specific CYP-mediated activities were diethyldithiocarbamate (100 μM; CYP2E1), sulphaphenazole (50 μM; CYP2C9), quinidine (10 μM; CYP2D6), midazolam (100 μM; CYP3A4), troleandomycine (100 μM; CYP3A4), 7-8 benzoflavone (10 μM; CYP1A1), coumarin (100 μM; CYP2A6) and orphenadrine (50 μM; CYP2B6), which are known to suppress more than 80% of the activities mediated by the CYP isoform given in parentheses.[23] Clotrimazole (50 μM) and *n*-octylamine (1 mM) were also used for their low specificity in inhibiting CYP-mediated activities. Specific immunoinhibitions were also performed, using purified rabbit polyclonal immunoglobulins (IgG) directed against rat NADPH-cytochrome P450 reductase. Rat liver NADPH-cytochrome P450 reductase was purified using the method described by Yasukoshi and Masters.[24] Immunological inhibition studies were assayed using 0.2 mg of microsomal protein preincubated with 10 mg of purified IgG for 30 min at 37°C. The NADPH-cytochrome P450 reductase activity was evaluated according to the method described by Masters and colleagues.[25] Purified IgG anti-rat NADPH-cytochrome P450 reductase was shown to inhibit 80%

of the cytochrome *c* reductase activity in human liver micosomes. Immunoinhibition against CYP2C9-dependent activity was also performed using serum from primary immunized rabbits by CYP2C9 obtained from yeast expressing the corresponding cDNA. Experimental conditions for immunoinhibition were identical. For each inhibited activity, control experiments were conducted under the same conditions with the same amount of methanol needed for solubilization of the inhibitor (1% final concentration) or with serum obtained from standard rabbits.

WESTERN BLOT ANALYSIS

Human hepatic microsomal fractions (2–100 µg protein) were subjected to immunoblotting as described previously,[26] using rabbit immunoglobulins against the main human CYP isoforms (that is, CYP1A2, 2C8, 2C9, 2D6, 2E1 and 3A4). The intensity of the bands was determined by laser densitometry using a densitometer (Scan Jet 2C, Hewlett Packard) linked to a microcomputer running Scan Analysis software. Various concentrations of liver microsomes were loaded on each gel to establish a standard curve. The amount of each CYP isoform was expressed in arbitrary units and compared with the specific content of the corresponding CYP isoform of the human liver fraction exhibiting the highest activity.

CDNA-EXPRESSED CYP ISOFORMS

Incubations with CYP expressed in recombinant yeast were also performed to assess the involvement of specific CYP isoforms in the production of 1,4-quinol. Transformed yeast were produced and microsomes were prepared as previously described.[27] Incubations were performed in a final volume of 1 ml (28°C, 30 min) containing yeast expressing one of the following human CYP isoforms (CYP1A1, 1A2, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 3A4 or 3A5: 200 pmol), cytochrome b_5 (200 pmol), 10 and 50 µM propofol, in a NADPH-regenerating system containing 10 mM $MgCl_2$. Microsomes from human lymphoblast cells expressing CYP2A6 (Gentest, Woburn, MA, USA) were also used under conditions recommended by the manufacturer (37°C, 30 min in Tris-HCl buffer 50 mM, pH 7.4).

The relationship between Western blot (or coumarin 7-hydroxylase activity) *versus* 1,4-quinol formation was calculated using a step-wise multiple regression performed in StatView software (Abaccus Concepts Inc., Berkeley, CA, USA), accepting $P < 0.05$ as significant. Statistical significance in inhibition studies was assessed using Student's *t* test with $P < 0.05$. Kinetic parameters (propofol concentration from 2 to 200 µM) were obtained by non-linear least squares regression. The minimum values of the sum of the squared residuals were computed using NAG Fundation Library routine E04FDF (Numerical Algorithms Group Ltd, The Math Works Inc., Natick, MA, USA).

Results

PROPOFOL HYDROXYLASE ACTIVITY

Human liver microsomes exhibited propofol hydroxylase activity (0.39 (0.20) nmol min^{-1} mg^{-1}) and 1,4-quinol was the only metabolite recovered. The mass spectrum of the metabolite peak was identical to that of authentic 1,4-quinol (data not shown). No other possible metabolite could be found in either the GC-MS system with or without silylation or in an HPLC system with UV detection. Furthermore, assays of propofol metabolism by measurement of the formation of 1,4-quinol or by measurement of propofol disappearance gave similar results. The interindividual variation in the rate of formation of the 1,4-quinol in the 12 different samples was no more than two-fold (0.66–1.30 nmol min^{-1} mg^{-1}). Incubations performed without an NADPH-generating system, or in the presence of clotrimazole, *n*-octylamine, or IgG anti-rat NADPH-cytochrome P450 reductase decreased the formation of 1,4-quinol by more than 80%. The conversion of propofol was linear over the protein concentration range 0.5–3 mg ml^{-1} and 0.2–1 mg ml^{-1}, for up to 20 min for 50 µM and 10 µM of propofol respectively. The propofol hydroxylase activity assayed with different concentrations of the substrate (2–200 µM), performed with microsomes from five human livers, exhibited Michaelis–Menten kinetics whose parameters were 18 µM (95% CI 15.1–20.1) and 2.6 nmol min^{-1} mg^{-1} (95% CI 2.45–2.68), for the apparent K_M and V_{max} values, respectively. An Eadie–Hofstee representation of these kinetics in HL3 microsomes is shown in fig. 1.

INVESTIGATIONS OF HUMAN LIVER CYP INVOLVED IN PROPOFOL HYDROXYLASE ACTIVITY

To characterize the involvement of liver-specific CYP in the metabolism of propofol, the rate of formation of 1,4-quinol by human microsomes was compared with their specific content of CYP isoforms (fig. 2). A stepwise multiple regression was performed to take into account the contribution of different CYP isoforms in propofol metabolism. Activities of all microsomal fractions obtained with a substrate concentration of 10 µM exhibited a significant correlation ($r = 0.78$, $P = 0.0076$) with the microsomal immunoquantified-content of CYP2C9. None of the other immunochemically-tested human CYP isoforms (that is, CYP1A2, 2C8, 2D6, 2E1, and 3A4)

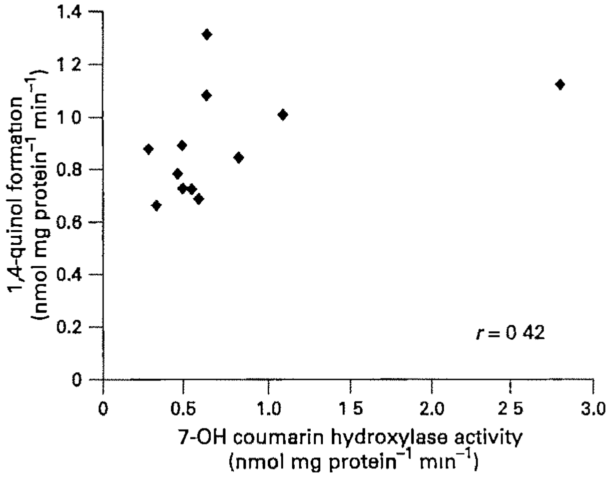

Figure 3 Correlation between the 7-OH coumarin hydroxylase activity and the formation of 2,6-diisopropyl-1,4-quinol by human liver microsomes. Each value is the mean of two separate assays.

Table 1 Formation of 2,6-diisopropyl-1,4-quinol by specific human cytochrome P450 (CYP) isoforms expressed in heterologous systems. Results represent the mean of duplicate or triplicate determinations. Incubations were performed with microsomes from transfected yeast or from human B-lymphoblastoid cells (*) incubated with 10 μM or 50 μM substrate concentration. ND=not determined

Recombinant human CYP isoforms	2,6-diisopropyl 1,4-quinol formation (nmol min^{-1} nmol P450^{-1})		V_{max}/K_m (mg min^{-1} nmol P450^{-1})
	(Propofol 10 μM)	(Propofol 50 μM)	
1A1	0.89	3.96	ND
1A2	0.12	1.84	0.011
2A6*	0.90	2.99	ND
2C8	0.26	1.10	0.016
2C9	1.24	5.65	0.118
2C18	0.25	1.36	ND
2C19	0.18	0.82	ND
2D6	<0.01	0.12	ND
2E1	<0.01	<0.01	ND
3A4	<0.01	0.04	0.0007
3A5	<0.01	<0.01	ND

Table 2 Effect of selective cytochrome P450 (CYP) inhibitors on the metabolism of propofol. COUM = coumarin; DDC = diethyldithiocarbamate; MID = midazolam; ORPH = orphenadrine; QUIN = quinidine; SULF = sulfaphenazole; TAO = troleandomycin; 7,8 bz = 7-8 benzoflavone; — = not performed. Results are expressed as percent inhibition

Liver	Propofol concentration (μM)	TAO (100 μM)	MID (100 μM)	SULF (50 μM)	COUM (100 μM)	ORPH (50 μM)	QUIN (10 μM)	DDC (100 μM)	7,8 BZ (10 μM)
HL3	10	—	—	23	—	—	—	—	0
	50	—	15	10	8	—	—	17	—
HL4	10	—	—	19	—	—	—	—	—
HL5	10	—	—	39	—	—	—	—	13
	50	9	12	1	29	25	0	9	8
HL7	10	—	—	25	—	—	—	—	5
	50	—	15	7	25	—	—	11	—
HL11	10	—	—	21	—	—	—	—	—

could be related to the specific activity of each microsome. Similarly, there was no significant correlation between the rate of formation of 1,4-quinol and the coumarin 7-hydroxylase activity (r = 0.42, fig. 3), a marker of CYP2A6-mediated activities, or total CYP content. When incubations were assessed with a higher concentration of propofol (50 μM), correlation between the rate of formation and CYP2C9 was not significant (r = 0.51).

Heterologous systems expressing 11 different CYP isoforms were used to assess the intrinsic ability of these isoforms to catalyse propofol. Results are shown in table 1. Microsomes from yeast expressing CYP2C9 exhibited a high activity for formation of 1,4-quinol. Lymphoblast cells expressing CYP2A6 were also reasonably active. Other cDNAs of CYP expressed in yeast (that is, CYP1A1, 2C8, 2C18, 2C19, or 1A2) produced the 1,4-quinol, at low concentration of substrate (10 μM). With an increase in the substrate concentration (50 μM), other isoforms hydroxylated propofol but the activities remained negligible. These concentrations are commonly observed in plasma after a single bolus for induction of anaesthesia,[2 28] although the actual intracellular concentration around the active sites is uncertain. Enzymatic efficency (V_{max}/K_M) of several isoforms was also determined (table 1), CYP2C9 exhibiting the highest rate.

Selective chemical CYP inhibitors were also used in this study to determine the potential roles of CYP isoforms in the metabolism of propofol (table 2). A moderate inhibition (around 25%) was observed in incubations performed, with a 10 μM concentration of propofol, with sulphaphenazole as a competitive inhibitor of CYP2C9 despite a broad inhibition of the tolbutamide hydroxylase activity under the same conditions. The percentage inhibition diminished when the concentration of the substrate was set at 50 μM. Similar inhibitions were found with coumarin (21%) or orphenadrine. No other agent tested significantly inhibited propofol hydroxylase activity.

Immunoinhibition assessed with IgG anti-CYP2C9, ranging from 25 to 75 μl of immune serum, exhibited a decrease in activity from 3.7% to 46.7% respectively (values are the mean of three assays performed separately in microsomes from three samples selected for their high response in immunoblot performed with anti-CYP2C9).

Discussion

In human microsomal fractions, 1,4-quinol was the single hydroxylated metabolite of propofol recovered. *In vivo* studies showed the presence of sulphate or glucuronide conjugates of propofol or of its hydroxylated metabolite: 1,4-quinol.[1 4] 1,4-quinol is the only identified hydroxylated metabolite of propofol and could represent as much as 47% of the total metabolism of propofol over 1 day.[1 4] Absence of an NADPH-generating system, or co-incubations with clotrimazole, n-octylamine or IgG anti-reductase from rat dramatically decrease the production of the 1,4-quinol indicating the activity of CYP in propofol metabolism. These results are complementary with those previously reported by Chen and colleagues, who observed that propofol competed with carbon monoxide for a common binding site on the haem moiety.[13] Propofol hydroxylation follows Michaelis–Menten kinetics and is consistent with the existence of a single active site or different catalytic sites with close affinities, because the existence of two or more CYP with similar affinities for propofol would not be distinguished in the kinetic studies. The K_M value is near physiological plasma concentrations.[2 29]

The present study clearly demonstrates the involvement of CYP2C9 in the metabolism of propofol. This conclusion is supported by several lines of evidence. A significant correlation between immunochemically determined CYP and the hydroxylation of propofol was confirmed only for CYP2C9 at a concentration (10 μM) near the value of the Michaelis–Menten constant. Similarly, immunoinhibition and CYP2C9 expressed in yeast confirm the participation of this isoform in the production of the 1,4-quinol, despite a weak inhibition of the activity in fractions coincubated with sulphaphenazole, a chemical inhibitor of CYP2C9-catalysed activities.[30] Although sulphaphenazole is an efficient inhibitor of reactions mediated by CYP2C9 with *Ki* values from 0.12 to 0.3 μM on tolbutamide hydroxylation,[30 31] it was unable to inhibit more than 39% of the production of 1,4-quinol. Nevertheless, some studies suggest the possible involvement of isoforms other than CYP2C9 in the metabolism of propofol. First, the linear regression of the relationship between the immunochemical reactivity of CYP2C9 and the production of 1,4-quinol has a *y*-intercept significantly different from zero (46% of residual activity compared with the mean of the activity). Second, immunological and chemical inhibitions decrease propofol hydroxylase activity, which remains below 50% of the control activity. Finally, correlation between the propofol hydroxylase activity determined with a substrate concentration of 50 μM and immunochemical-CYP2C9 reactivity was not significant despite a two-fold increase in this activity (data not shown). These data suggest the participation of several isoforms, which should account for the remaining activity at therapeutic concentrations. Microsomes prepared from cells containing various CYP isoforms were used to support these arguments. Thus, microsomes from cells expressing CYP2A6 or 1A1 raised to a high propofol hydroxylase activity even at low substrate concentrations as well as several isoforms (that is, 2C8, 2C18, 2C19, 1A2) that exhibited a lower activity and a low enzymatic efficiency. These heterologous systems provide evidence on the intrinsic capacity of a specific isoform to catalyze the reaction[32 33] and strongly suggest *in vivo* participation if the expression level in organs or tissues involved in the metabolic pathways of the drug, or the concentration of the drug around the active site, or both, are sufficient.[34] Nevertheless, the involvement of these isoforms in metabolic pathways may be overestimated. Thus, when we focus on the effective involvement of these isoforms in microsomal fractions, all results are inconclusive. This may be the consequence of a low expression of these specific isoforms in the microsomal fractions (for example, CYP1A1 is usually expressed in liver at very low level, CYP2A6 accounts for about 4% of total CYP) or a narrow range of levels of some CYP isoforms in our liver bank (especially 2A6, 3A4).

Many investigators have studied the possible interaction between propofol and other anaesthetic drugs such as alfentanil and derivatives[12 13 15 35] or enflurane[11] because these compounds are often associated in anaesthetic procedures. Previous studies in humans did not show any pharmacokinetic interactions between propofol and fentanyl[36] or propofol and alfentanil.[35] However, Janicki and colleagues showed a decrease in the *in vitro* oxidative metabolism of alfentanil and sufentanil by propofol.[12] The metabolic transformation of these opioids is primarily mediated by CYP3A4.[37 38] Furthermore, the present study shows a low participation of 3A4 even at high concentrations of propofol. Nevertheless, these data do not rule out a possible interaction between propofol and this isoform that might explain the interaction observed by Janicki and colleagues. In contrast, other authors showed, in rabbits, that pretreatment with cimetidine, an inhibitor of CYP3A4-mediated activities,[39] did not affect the *in vitro* rate of propofol elimination.[9] Our study also clearly shows that CYP2E1 is not involved in propofol metabolism at low substrate concentration as was previously observed in rats by Baker and colleagues.[11] Nevertheless, some authors have observed an *in vitro* concentration-dependent inhibitory effect of propofol on CYP2E1-mediated activities in hamster and in human.[13 15] These discrepancies may also be explained by the difference in the substrate concentration, because inhibition studies in human microsomes were performed with 0.5 and 1 mM, concentrations that are not clinically relevant.[13] In the same way, earlier *in vivo* studies showed that the plasma concentrations of propofol were higher in patients pretreated with fentanyl.[6] It seems that this kind of interaction may be related to an inhibition of the two compounds on the glucuronidation pathways[8] rather than to a direct interaction on CYP. *In vitro* inhibition by propofol of the glucuronidation of propranolol has already been observed.[40 41] Nevertheless, the rarity of the interactions occurring between clinically used drugs and propofol may be explained by other events. First, glucuronidation which is a major pathway of the metabolism of propofol may be catalysed by different isoforms of UDP-glucuronosyltransferases and the latter are known to exhibit a broad specificity towards a large number of compounds.[8 42 43] Secondly, the hepatic extraction coefficient for propofol is very high.

In conclusion, CYP2C9 is involved, by at least 50%, in the oxidative metabolism of propofol, particularly at low substrate concentration. Other isoforms, such as CYP2A6, 2C8, 2C18, 2C19 and 1A2, are also involved in this metabolism but the characterization of their relative activities remains difficult. It can be postulated that the increase in propofol concentration or the defect of CYP2C9 contributes to the participation of this CYPs, or promotes the glucuronidation, a pathway known to be of low specificity and high capacity.[8] From the clinical point of view, the contribution of multiple isoforms in a metabolic pathway of a highly metabolized therapeutic agent might be desirable because its metabolism is not affected by polymorphism and is less affected by metabolic interactions with other drugs, except in individuals expressing a high proportion of one of these isoforms.

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Evaluation of a new design of tracheal tube cuff to prevent leakage of fluid to the lungs

P. J. YOUNG, S. A. RIDLEY, G. DOWNWARD

Summary

A new design of tracheal tube cuff was compared with two types of high-volume, low-pressure (HVLP) cuffed tracheal tube for leakage of fluid from the subglottic space into the trachea. Spontaneous and positive-pressure ventilation were simulated using a mechanical lung, an intubated model trachea and a ventilator. Excised human tracheas were intubated and leakage past the cuff assessed. Distention of the tracheal wall was measured. HVLP cuffs leaked rapidly in the model during all modes of ventilation, and also in the excised human tracheas. This leakage occurred preferentially down longitudinal folds that occur in the HVLP cuff wall. The new design completely prevented leakage in the model during all modes of ventilation, during tracheal suctioning, and with tube movement. The new cuff also prevented leakage in the excised human tracheas. Tracheal wall distention and tracheal wall pressures were similar for all cuffs tested. (*Br. J. Anaesth.* 1998; **80**: 796–799)

Keywords: cuff tracheal tube; intubation tracheal; pneumonia aspiration; pneumonia ventilator-associated

A tracheal tube with a high-volume low-pressure (HVLP) cuff does not protect the lower airway from contamination by material leaking from the subglottis to the trachea below.[1 2] Subclinical leakage of contaminated secretions around the cuff occurs in mechanically ventilated patients on the intensive care unit (ICU), causing tracheal colonization and increasing the risk of ventilator-associated pneumonia.[3] Such leakage occurs in 100% of cases during anaesthesia, down longitudinal folds within the cuff wall.[2] These folds generally occur in an HVLP cuff on inflation within the trachea, as the diameter of the cuff is greater than that of the trachea, and the intracuff pressure is equal to the tracheal wall pressure. Low-volume high-pressure (LVHP) cuffs provide complete protection against leakage[2] but are unfortunately associated with high tracheal wall pressures that predispose to injury.[4]

A new design of cuff that offers the protection against leakage provided by the LVHP cuffs, and the protection against excessive tracheal wall pressures that is provided by the HVLP cuffs, would be advantageous. Such protection against leakage could be achieved by designing the cuff so that no folds form in the cuff wall. We describe a new cuff made from latex with inflation characteristics that allow the tracheal wall pressure to remain constant.

We compared standard HVLP cuffed tracheal tubes with the new design of cuffed tube in a model and excised human tracheas, for leakage of fluid past the cuff into the trachea and for tracheal distention and pressure exerted on the model tracheal wall.

Materials and methods

NEW PRESSURE-LIMITED CUFF

Manufacture

The cuff is removed from a standard tracheal tube (Portex profile, 8 mm internal diameter). A hypoallergenic latex cuff is bonded, at stretch in line with the longitudinal axis of the tracheal tube, in the position of the original cuff. The new pressure-limited cuff is made by cutting a tube of latex from the small finger from a surgical glove (for example, Gammex, size 6.0, Ansell Medical). Tissue glue (Histoacryl, Braun) is used to bond the latex tube, under longitudinal tension, to the standard tracheal tube so that a new cuff is formed.

Physical characteristics of cuff (outside trachea)

As air is injected through the pilot valve, the cuff diameter increases and the intracuff pressure increases. The pressure–diameter relationship is critical to the function of the cuff. During manufacture the cuff is bonded to the tube at stretch so that the intracuff pressure stays nearly constant (forms a plateau) over the entire range of expected tracheal diameters (fig 1). The range of tracheal diameters (1.4–2.7 cm) was derived from published data of adult tracheal circumferences.[5]

Physical characteristics of cuff (inside trachea)

When the cuff is inflated progressively inside a trachea of unknown diameter, the intracuff pressure increases quickly to its plateau while the volume continues to increase at constant pressure. The plateau

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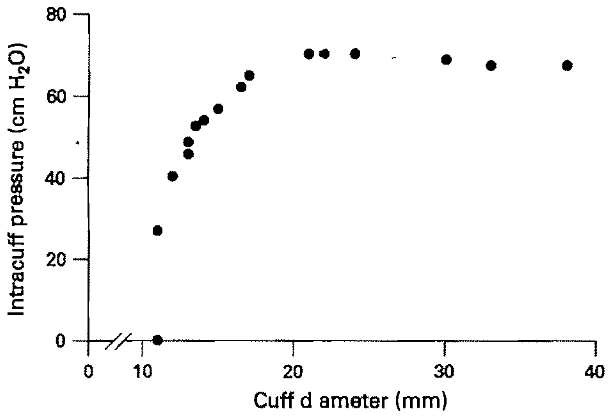

Figure 1 The relationship of intracuff pressure and cuff diameter for a pressure limited cuff (outside the trachea).

pressure is approximately 65–70 cm H_2O using a cuff 4.5 cm long. Plateau pressure in this range has been consistently achieved in more than 40 pressure-limited tubes we have manufactured. During inflation the cuff wall will touch the tracheal wall, and the intracuff pressure will start to increase above the plateau pressure. The tracheal wall pressure will then increase at the same rate. The cuff inflation is limited to 30 cm H_2O above the plateau pressure (that is 95–100 cm H_2O using the 4.5 cm cuff). This provides a wall pressure of 30 cm H_2O at all tracheal diameters.

VENTILATORY MODEL WITH MODEL TRACHEA

Lung/trachea model

The model has been described previously[6] and consists of an intubated model trachea ventilating a model lung (fig. 2).

Experimental plan

The artificial trachea was intubated in turn with full-length (32 cm); size 8 mm internal diameter tubes of three types: Portex profile, Mallinckrodt HiLo, or the new pressure-limited cuff. The intracuff pressure was set manually at 30 cm H_2O with a cuff inflator (Monitor control inflator, VBM, Medizintechnik) for the HVLP cuffs, and at 30 cm H_2O above the plateau for the new pressure-limited cuff.

The proximal tracheal tube was then connected to a Bird ventilator (6400ST volume ventilator). Three ml of water was instilled into the space above the cuff to represent the subglottic space and the trachea was observed for any leakage of the water.

Modes evaluated

Spontaneous ventilation was simulated by driving the model lung mechanically with the proximal tracheal tube disconnected. A tidal volume of 600 ml, a frequency of 12 breaths min^{-1} and an I:E ratio of 1:2 was used. Intermittent positive pressure ventilation (IPPV) was simulated by ventilating the model lung through the trachea tube with a tidal volume of 600 ml, a frequency of 12 breaths min^{-1} and an I:E ratio of 1:2. The compliance of the model lung was altered to achieve peak inflation pressures of 40 cm H_2O at the ventilator (10 cm H_2O higher than the cuff pressure).

Each ventilatory mode was tested over a 24-h period or until all of the 3 ml of water had leaked.

The effect of tracheal suctioning was also tested (using high-pressure suction from a hospital pipeline with a Clement's adapter, which generated a maximum negative pressure of 400 mm Hg) with suction (through a 14CH catheter). The catheter was advanced to 5 cm beyond the tracheal tube tip, then withdrawn over a 6-s period under suction.

Tracheal tube movement was tested with 10 vertical 5-cm movements, and 10 rotations through 45 degree over a 5-min period.

Cuffs tested

A single sample of Portex profile, a Mallinckrodt HiLo and a new pressure-limited cuff were used, all

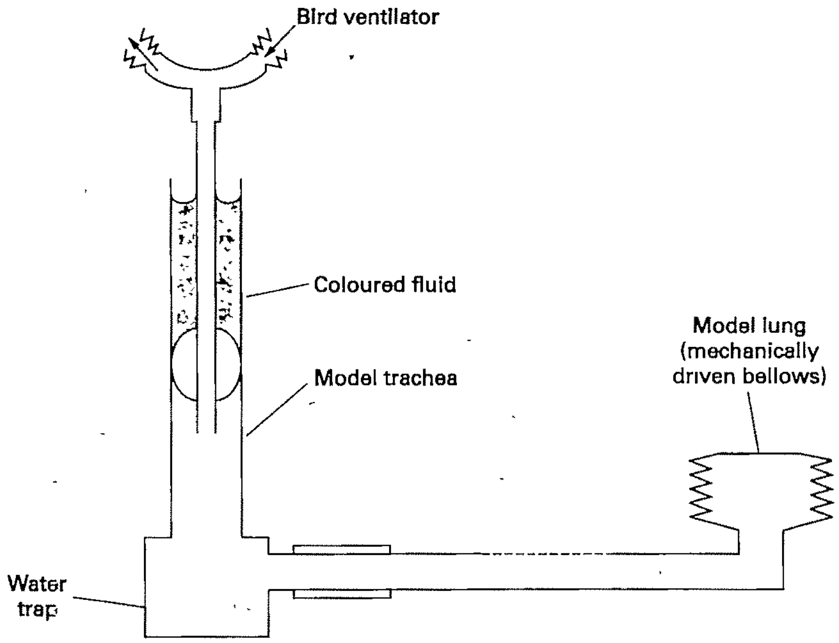

Figure 2 Diagram of model trachea and lung layout.

8 mm internal diameter. All observations were repeated five times.

Excised human trachea

The tracheas from four human subjects within 72 h of death were dissected by a pathologist from larynx to carina (with the oesophagus left in place). The tracheas were suspended vertically and intubated with a Portex profile, 8 mm internal diameter, and then the pressure-limited cuff. The tracheas were intubated within 9 cm from the tube tip to the cords (the dark line on the Portex tube at the level of the cords).

The intracuff pressure was set at 30 cm H_2O manually with a cuff inflator for the HVLP cuffs, and 30 cm H_2O above plateau for the new pressure-limited cuff tube (95 cm H_2O).

The anteroposterior and lateral external diameters were measured with a caliper before and after cuff inflation, at the level of the cuff. Three ml of water were added above the cuff and observed for leakage.

WALL PRESSURE MEASUREMENT

The wall pressure was measured in two cylinders with internal diameters of 2.2 and 2.6 cm. The lateral pressure was measured by inflating the cuff within the cylinder to 130 cm H_2O (measured directly with a mercury column) and filling the cylinder above the cuff with water to 70 cm. The intracuff pressure was then reduced in a stepwise fashion until leakage began. When leakage had stopped, a second observer blind to the intracuff pressure used a mounted meter rule and set square to measure the height of fluid retained above the cuff.

The water column is thus used as a manometer. Hydraulic pressure exerts its effect in all directions equally. If the water column above the cuff exerts a pressure greater than the lateral pressure of the cuff on the cylinder wall, then water will leak through until the water column pressure and lateral pressure are equal.

STATISTICAL ANALYSIS

We used the Mood median test to examine differences in leakage past the cuff and linear regression analysis to examine the relationship between cuff and tracheal wall pressures. $P=0.05$ was considered significant. The statistical analysis was performed on an IBM-compatible computer using Minitab statistical software.

Results

VENTILATORY MODEL

In the model trachea both the Portex and Mallinckrodt HVLP cuffs allowed free leakage of fluid past the cuff. All 3 ml leaked past the cuff within 1 min with all ventilatory modes tested. This leakage was seen to occur along the folds in the cuff wall. There was no leakage when the new pressure-limited cuff was used during spontaneous ventilation, IPPV, tracheal suctioning and during movement of the tube in the model trachea (Chi-square=60, df=2, $P<$ 0.001). No leakage was observed with the pressure-limited cuff over the 24 tested for each ventilatory mode.

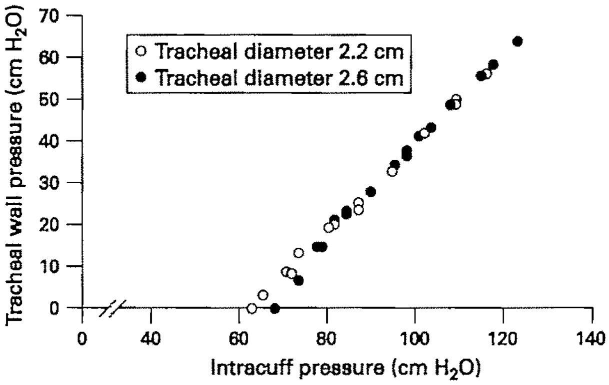

Figure 3 Relationship of wall pressure and intracuff pressure for a pressure-limited cuff placed in a model trachea of diameter 2.2 cm or 2.6 cm.

EXCISED HUMAN TRACHEA

There was no difference between the increase in tracheal wall anteroposterior or lateral external diameter between the Portex cuff and the pressure-limited cuff (2.4 mm and 1.9 mm increase respectively in anteroposterior diameter; 0.8 mm and 0.6 mm increase respectively in lateral external diameter) after inflation.

Leakage was seen with the HVLP cuff. All 3 ml of fluid leaked past the cuff within 1 min. There was no leakage observed over a 10-min period with the new pressure-limited cuff cuff in the four tracheas studied (chi-square=8, df=1, $P<0.005$).

WALL PRESSURE RESULTS

The wall pressures maintained a linear relationship to intracuff pressure with a slope of 1.06 and an x axis intersection of 63.0 cm H_2O for the 2.2 cm diameter cylinder, and a slope of 1.15 and an x axis intersection of 65.7 cm H_2O for the 2.6 cm diameter cylinder (fig. 3).

Discussion

Leakage of fluid past tracheal tube cuffs has been recognized as a problem in anaesthesia with HVLP cuffs for more than 20 years.[1] Leakage past the cuff is considered a major cause of ventilator-associated pneumonia (VAP) in the intensive care unit.[3] In patients with previously healthy lungs ventilated in the intensive care unit, the lower respiratory tract often becomes colonized with bacteria. Several of these patients acquire VAP, which is caused by factors such as altered host defences, acquisition of pathogenic bacteria in the upper gastrointestinal and respiratory tracts, increased exposure of lung tissue to these bacteria, and impaired host clearance.[7]

Adult intensive-care patients receiving mechanical ventilation have an incidence of VAP of 20–60%[8] and a mortality reported at 27%.[9]

A tracheal tube that reduces or eliminates leakage from the pharynx to the lungs could have an important part to play in the reduction of VAP. A tube designed with a dorsal separate channel allowing subglottic secretion drainage (Hi-Lo EVAC; Mallinckrodt) halved the incidence of VAP using both intermittent[10] and continuous drainage.[11] This method of drainage is likely to reduce but not prevent oropharyngeal secretions leaking into the lung. One would expect that complete prevention of leakage would lead to a further reduction in the incidence of VAP. Kolobow describes a “no-pressure” laryngeal seal design that uses a series of compliant gills rather than a cuff in an attempt to prevent leakage from subglottis to trachea and to minimize airway injury.[12] This tube prevents the passage of oropharyngeal secretions to the lungs in sheep when methylene blue is placed in the oropharynx as a marker.[13]

The slope of the wall pressure and intracuff pressure graph for the pressure-limited cuff tube is close to unity (fig. 3) and the x axis intersection is close to the plateau pressure of the cuff, that is 65–70 cm H_2O (fig. 1), indicating that in the cylinders tested tracheal wall pressure can be derived from intracuff pressure measurements. This plateau pressure varies minimally (within the range of 5 cm H_2O) over time and usage of the tube. Hence inflation of the cuff to a predetermined pressure should generate a wall pressure that is within the acceptable range.

The pressure-limited cuff tube has the advantage of being cheap and simple to manufacture from materials used commonly in anaesthetic and surgical practice, and its function in the benchtop models is excellent. The glove material is biocompatible (EN30993 Part 1). The pressure-limited cuff tube will require further validation in human studies, and a pilot study of the cuff is underway on our intensive care unit to compare the new cuff and an HVLP cuff with respect to tracheal colonization and ventilator-associated pneumonia. The present study introduces a new concept in the design of a tracheal tube cuff, in an attempt to prevent the soiling of the trachea in patients whose lungs are ventilated. For this new tube to be of use clinically, it is necessary that the cuff remains inflated above its plateau pressure at all times.

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Synergistic antinociceptive interaction between sevoflurane and intrathecal fentanyl in dogs

D. Ma, S. M. Sapsed-Byrne, M. K. Chakrabarti, J. G. Whitwam

Summary

This study determined the nature of the antinociceptive interaction between sevoflurane and intrathecal fentanyl on somatosympathetic reflexes in anaesthetized dogs. Afferent Aδ- and C-fibre-mediated somatosympathetic reflexes, evoked by supramaximal electrical stimulation of tibial nerves, were recorded from renal sympathetic nerves. The effect of fentanyl alone, administered intrathecally (i.t.) in incremental doses from 2 to 64 µg, was compared with the effect of the same doses during the administration of 1.5% sevoflurane. The mean ED_{50}s for the depressant effect of fentanyl (i.t.) on Aδ and C reflexes were 35.6 µg and 14.2 µg while 1.5% sevoflurane, when administered alone, depressed them by 15.5% ($P < 0.05$) and 27.5% ($P < 0.01$) respectively. During the administration of 1.5% sevoflurane, the mean ED_{50}s of fentanyl (i.t.) for the depression of Aδ and C reflexes were reduced by 76% and 75%, to 8.5 µg and 3.5 µg respectively. The combined antinociceptive effects of sevoflurane and intrathecal fentanyl were not additive but exhibited a high degree of synergistic interaction. (*Br. J. Anaesth.* 1998; **80**: 800–806)

Keywords: anaesthetics volatile sevoflurane; analgesics opioid fentanyl; reflexes somatosympathetic; interactions (drug) synergy; dog

In the 1970s it was shown that the intrathecal (i.t.) administration of opioids could provide pain relief.[1 2] These studies contributed to our understanding of the regional role of opioid receptors, which are found not only in supraspinal centres but also, for example, in the dorsal horn of the spinal cord on the terminals of small-diameter primary afferent fibres.[3–5] Recent work has suggested that the spinal cord is one of the principal sites of action of inhalation anaesthetic agents,[6–9] and this has been summarized by Eger and associates.[10] Although previous studies have shown that opioids administered spinally can reduce the minimum alveolar concentration (MAC) of inhalation agents in humans and animals[11–14] the nature of their combined effect, that is whether additive or interactive, has not been investigated. We have tested the hypothesis that an inhalation anaesthetic and an opioid administered intrathecally act synergistically to depress nociceptive responses.

Single supramaximal electrical stimuli applied to somatic nerves evoke two bursts of activity in sympathetic nerves because of the activation of both afferent myelinated (group III or Aδ) and unmyelinated (group IV or C) fibres.[15] These reflexes are called "somatosympathetic reflexes". They can be used to evaluate the antinociceptive effects of drugs[16] and are important in the management of anaesthetized, paralysed and ventilated patients. Unsynchronized stimulation of Aδ and C fibres provides the variable nociceptive responses to surgical trauma. A controlled input by electrical stimulation of a specific nerve allows the relative quantitative effects of drugs on the Aδ and C components of nociception to be compared. In the present study, Aδ- and C-fibre mediated somatosympathetic reflexes were used as nociceptive indices to examine the type of interaction between sevoflurane and fentanyl administered intrathecally in anaesthetized dogs.

Materials and methods

GENERAL PROCEDURE

The study was approved by the UK Home Office (Licence PPL 90/00852). We studied 16 beagles weighing 13.5–17 kg. Background anaesthesia was induced with methohexitone (Eli Lilly, UK) 10–15 mg kg^{-1} i.v. and maintained with 1% α-chloralose (Sigma, Poole, Dorset, UK) in an initial bolus dose of 30 mg kg^{-1} i.v., followed by a continuous infusion of 15-20 mg kg^{-1} h^{-1} i.v. The trachea was intubated and the lungs ventilated with oxygen-enriched air (HV 2000, SLE Ltd, Croydon, UK). Muscle paralysis was maintained using suxamethonium (Wellcome, Crewe, Cheshire, UK) 10 mg i.v. every 20–30 min. The cephalic vein in the right foreleg was cannulated for the administration of drugs and the infusion of fluids. The left femoral artery was cannulated for recording arterial pressure and sampling blood. Oesophageal temperature was measured with a thermistor (Yellow Springs Instruments, OH, USA) and maintained at 37–39°C by a heater in the operating table. Arterial blood gas tensions and pHa were determined regularly using a blood gas analyser (Radiometer ABL 3, Copenhagen, Denmark). pHa and Pa_{CO_2} were kept within normal limits, that is, 7.30–7.40 and 4.8-5.6 kPa respectively, and the Pa_{O_2} at 22.7-26.7 kPa; all three were kept close

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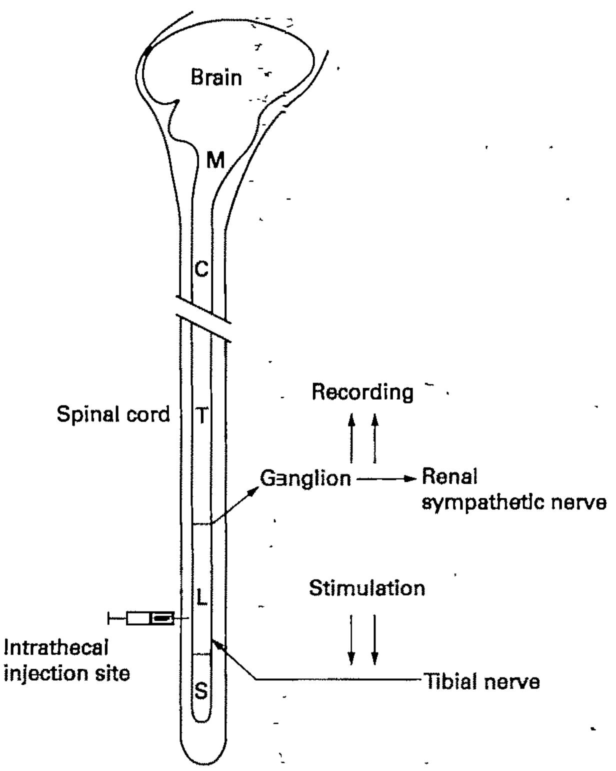

Figure 1 Schematic diagram of the preparation. M = Medulla; C = Cervical; T = Thoracic; L = Lumbar; S = Sacral.

to the control values in each preparation by small changes in the $F_{I_{O_2}}$ and ventilation, and occasional administration of small amounts of sodium bicarbonate. Heart rate and mean arterial blood pressure (MAP) were recorded continuously (Maclab 8 ADInstruments, ADInstruments Pty Ltd, Australia).

Each preparation was maintained in a left lateral position. The tibial nerve in the right hindleg was exposed in the upper to middle part of the thigh. A portion was dissected free of the surrounding tissues and a short section (≈2 cm) was desheathed, cut distally and mounted on silver–silver chloride electrodes for stimulation. The renal sympathetic nerves were exposed retroperitoneally alongside the renal artery; a single fascicle was desheathed and cut distally, near the kidney, and mounted on silver–silver chloride electrodes for recording sympathetic activity. Prepared nerves were immersed in mineral oil pools. For intrathecal injection of drugs a 22 gauge Y-can cannula (Wallace, Essex, UK) was inserted into the subarachnoid space through the dura exposed by laminectomy at L2–L3. Sevoflurane (Abbott Laboratories Ltd, Queensborough, UK) was administered with a Blease vaporizer (Chesham, Bucks, UK). The expired concentrations were monitored with a Capnomac II (Datex, Helsinki, Finland) which was calibrated before each experiment with standard gas. Twenty min was allowed for equilibration at each concentration. The schema of the preparation is shown in fig. 1.

MEASUREMENTS OF EVOKED AND SPONTANEOUS SYMPATHETIC ACTIVITY

Single supramaximal electrical stimuli (frequency 0.33 Hz, intensity 30 V, duration 0.5 ms) were applied to the tibial nerves by a stimulator (Grass S88, Quincy, MA, USA) with a matching isolation unit (Grass 478A). Efferent activity in renal sympathetic nerves was processed through a preamplifier (Tektronix type 122) and displayed on a dual-beam oscilloscope (Textronix type 565). Spontaneous sympathetic activity was subjected to full-wave rectification and then integrated with a time constant of 100 ms (Neurolog NL 90). The evoked somatosympathetic responses in renal sympathetic nerves were averaged (×16), rectified, and integrated using a neurolog system (NL 90, Digitimer, Welwyn Garden City, UK). Directly recorded and processed signals were displayed on an oscilloscope and also, when required, as "hard" copy on a thermal recorder (Gould 1602). The total electrical activity in the integrated signals of the rectified and averaged evoked sympathetic responses, and also the spontaneous sympathetic outflow during 20-s periods, was measured in arbitrary units. Data were based on the average of three sets of measurements at each point in each preparation and were expressed as a percentage of control values.

EXPERIMENTAL DESIGN

The preparation was allowed to stabilize for at least 30 min after completion of surgery, before control measurements were made; these were repeated 30 min later to ensure that the preparation was stable. Three groups of data were obtained for spontaneous sympathetic activity, and Aδ and C somatosympathetic reflexes evoked by tibial nerve stimulation: (1) the effect of intrathecal (i.t.) fentanyl alone; (2) the effect of sevoflurane alone, principally to determine accurately the ED$_{50}$ concentrations for both Aδ and C reflexes and also the effect of a concentration of 1.5%; (3) the effect of fentanyl (i.t.) during administration of 1.5% sevoflurane.

DRUG ADMINISTRATION

In five preparations, fentanyl (i.t.) (50 µg ml^{-1}) (Evans, Horsham, Sussex, UK) was administered in incremental doses of 2, 2, 4, 8, and 16 µg, each in 0.5 ml of saline (0.9%), followed by 32 µg in 1 ml and 64 µg in 2 ml of saline with 10 min intervals between doses.

In another five preparations, the ED$_{50}$s for the concentrations of sevoflurane that reduced the Aδ and C reflexes to tibial nerve stimulation by 50% were determined. This was done by first obtaining control values for these reflexes in the absence of sevoflurane, which was then administered to an equilibrated end-tidal concentration of 2.6%. (This had been shown in a previous study to depress the mean C response to radial nerve stimulation by 50%.[17]) Then, in the present study the "up-and-down" method with step changes of 0.2% was used to titrate accurately the ED$_{50}$ concentration for depression of the C response to tibial nerve stimulation. The end tidal concentration of sevoflurane was then increased to 3.7% (which had been shown previously to be the ED$_{50}$ for the Aδ response to radial nerve stimulation,[5] and the accurate ED$_{50}$ for depression of the Aδ response to tibial nerve stimulation was determined using similar methods. These values, together with the ED$_{50}$ of intrathecal fentanyl alone, were used to construct isobolograms for the combined effects of the two drugs (fig. 5).

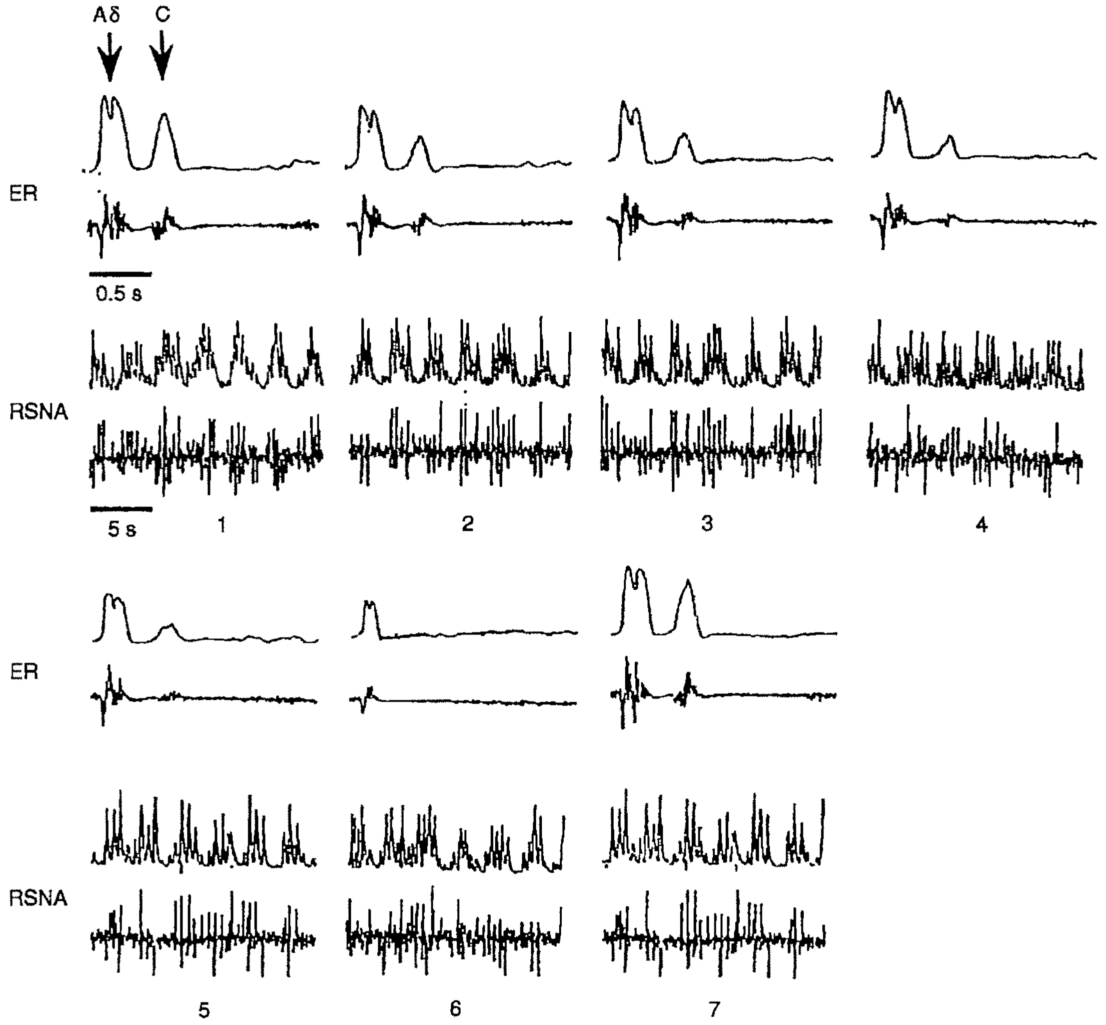

Figure 2 Typical recordings of the effects of fentanyl administered intrathecally on evoked responses (ER) and spontaneous sympathetic activity (RSNA) in renal nerves. ER: lower traces = average transient of 16 responses; upper traces = rectified integral of the averaged signals. RSNA: lower traces = transient amplified signals; upper traces = rectified and integrated signals. 1 = control; 2, 3, 4, 5, 6 = recordings at total cumulative doses of fentanyl of 8, 16, 32, 64 and 128 µg; 7 = 5 min after naloxone (2 mg i.v.).

In another six preparations, control values were first obtained for spontaneous sympathetic activity and Aδ and C somatosympathetic reflexes evoked by tibial nerve stimulation, in the absence of both the inhalation agent and intrathecal fentanyl. Sevoflurane was then administered in a concentration of 1.5%. (A previous study had shown that sevoflurane at this concentration reduced C reflexes in response to radial nerve stimulation by around 30%,[17] and also that its effects on somatosympathetic reflexes remained unchanged during observations lasting more than 3 h.) The effect of an equilibrated concentration of 1.5% sevoflurane on Aδ and C sympathetic reflexes evoked by stimulation of the tibial nerve was observed, stability of the preparation confirmed for 20 min, and new "control" data obtained showing the depressant effect of 1.5% sevoflurane (figs 3 and 4B). Fentanyl (i.t.) was then administered in doses of 2, 2, 4, 8, 16 and 32 µg at 10 min intervals until Aδ and C reflexes were abolished as described above for fentanyl alone. When the effect of the last dose of fentanyl had been recorded sevoflurane was withdrawn and measurements were repeated 30 min later.

At the end of each experiment, naloxone (2 mg i.v.) was administered to reverse the effects of fentanyl; return of the reflexes to control levels indicated that during the experiment there had been no damage to the spinal cord and no deterioration in recording. Finally i.t. injection of 2 ml plain lignocaine (2%) rapidly abolished not only the tibial nerve reflexes but also efferent spontaneous sympathetic activity, indicating that the spread of the potential effect of the injections of fentanyl encompassed both afferent fibres in the tibial nerve and the efferent sympathetic fibres from which recordings were made.

ANALYSIS OF DATA

All data are expressed as mean (SD). Statistical analysis was performed by analysis of variance (ANOVA) followed, when there were significant changes, by paired *t* tests. Differences were considered statistically significant when the P was < 0.05. A regression analysis was used to calculate the slope and 95% confidence intervals of the fentanyl (i.t.) dose–response curves using a computer program Statview + Graphic (Macintosh, Abacus Concepts, Berkeley, CA, USA); the $ED_{25,50,75}$ values, together with the 95% confidence intervals for fentanyl's depressive effects, were calculated from the dose-response curves.

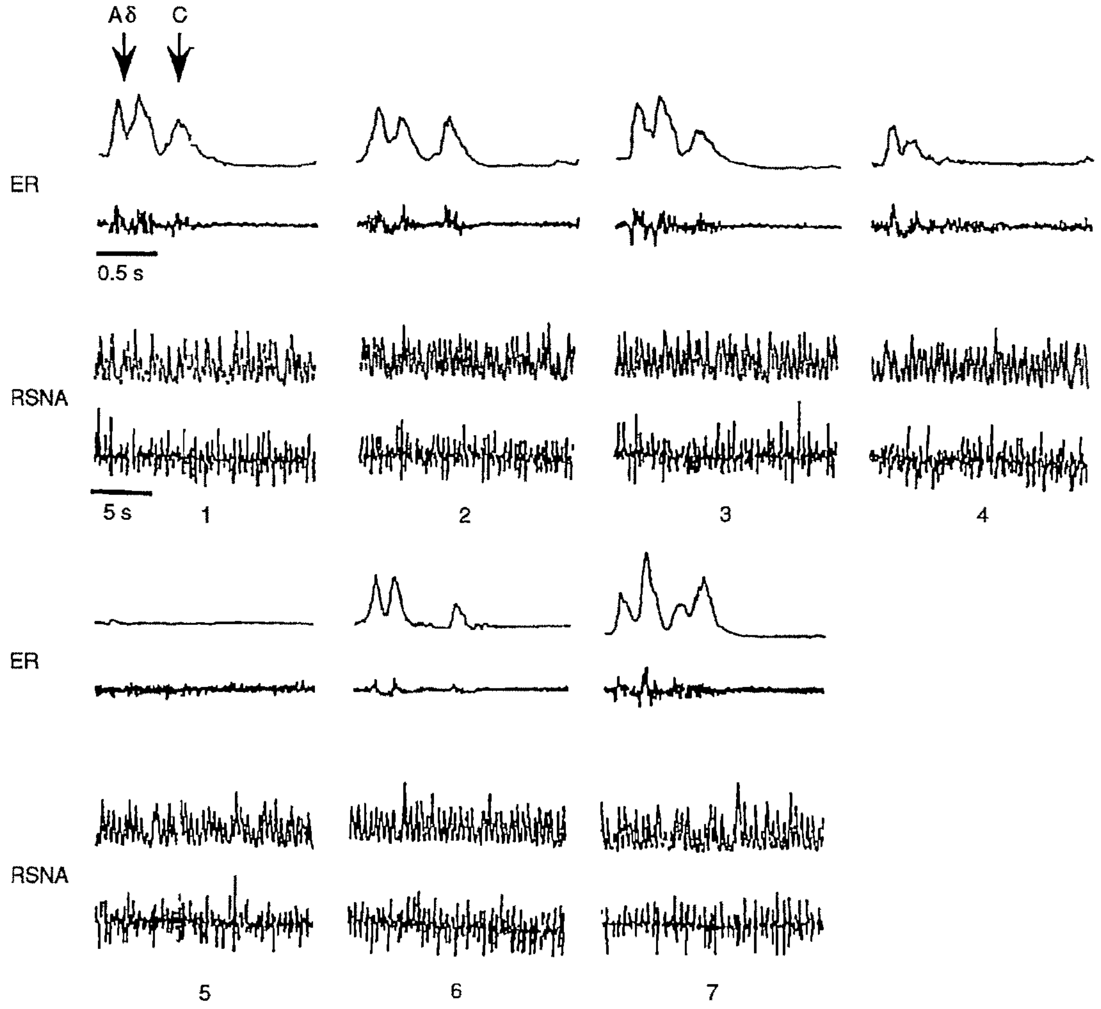

Figure 3 Recordings of the effects of fentanyl administered intrathecally, during the administration of 1.5% sevoflurane, on evoked responses (ER) and spontaneous sympathetic activity (RSNA) in renal nerves. ER: lower traces = average transient of 16 responses; upper traces = rectified integral of the averaged signals. RSNA: lower traces = transient amplified signals; upper traces = rectified and integrated signals. 1 = control; 2 = 20 min after 1.5 % sevoflurane administration; 3,4,5 = recordings at total cumulative doses of 16, 32 and 64 μg fentanyl i.t. combined with continued sevoflurane administration (1.5%); 6 = 30 min after sevoflurane withdrawal; 7 = 5 min after naloxone (2 mg i.v).

Results

Figures 2 and 3 show examples of typical recordings of spontaneous sympathetic activity and Aδ- and C-fibre-mediated somatosympathetic reflexes, evoked by supramaximal electrical stimulation of the tibial nerves, from two preparations. They show that whereas sevoflurane causes a major increase in the effect of i.t. fentanyl on somatosympathetic reflexes, there was no measurable effect on spontaneous sympathetic activity attributable to fentanyl and sevoflurane alone or in combination.

SOMATOSYMPATHETIC REFLEXES: SEVOFLURANE

ED$_{50}$ for Aδ and C reflexes

The mean ED$_{50}$s with 95% confidence intervals were 3.8 (3.5–4.4) % and 2.7 (2.4–3.0) % for Aδ and C reflexes respectively. These values are slightly higher than those for Aδ (3.7%) and C reflexes (2.6%) evoked by radial nerve stimulation,[17] which could be because of the larger size of the tibial nerve and the different site of access of the nerve fibres to the spinal cord.

Effect of 1.5% sevoflurane

Mean Aδ and C evoked responses were depressed to 84.5% ($P < 0.05$) and 72.5% ($P < 0.001$) of baseline by 1.5% sevoflurane (figs 3 and 4B). This confirms the results of a previous study, which showed that the differentially greater effect of sevoflurane on C reflexes compared with Aδ reflexes was comparable to that of μ opioids.[17]

SOMATOSYMPATHETIC REFLEXES: FENTANYL

Both C- and Aδ-evoked responses were depressed by fentanyl in a dose-dependent manner. It can be seen in figs 2 and 4A that fentanyl has a greater effect on C reflexes compared with Aδ and the ratio of the mean doses required to cause the same percentage reduction in C and Aδ responses was approximately 1:2.5. However at a total dose of 128 μg the C reflexes were completely abolished while the mean value of Aδ responses was reduced to 10% of control, with complete abolition in two of five preparations. Naloxone (2 mg i.v.) reversed the effects of fentanyl on both C and Aδ reflexes. Its ED$_{25,50,75}$, calculated from the dose response curves, for Aδ reflexes were

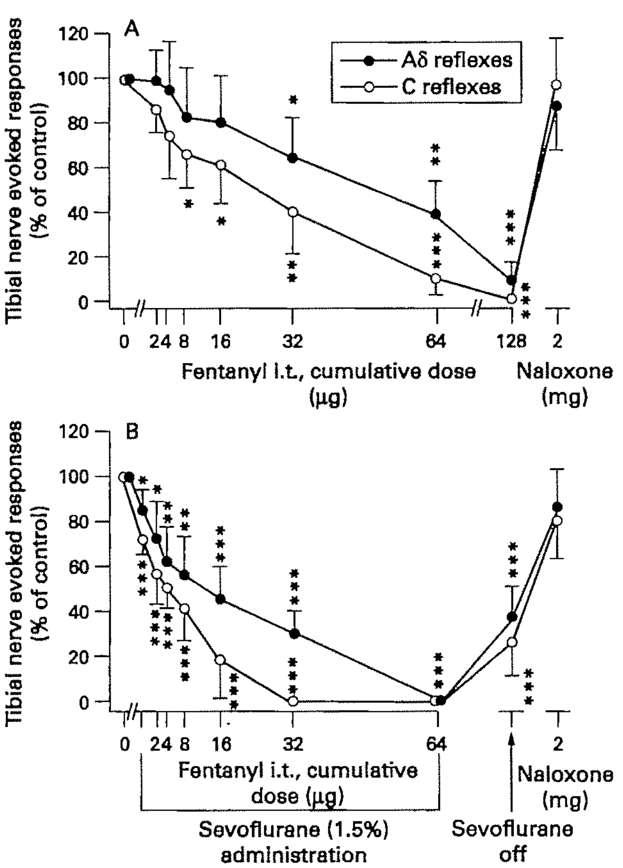

Figure 4 The effect of i.t. fentanyl alone (A, $n = 5$) and i.t. fentanyl combined with sevoflurane (1.5%) (B, $n = 6$) on Aδ- and C-fibre mediated somatosympathetic reflexes evoked by supramaximal electrical stimuli (30 V intensity, 0.5 ms duration, 0.33 Hz frequency) of tibial nerves. Results are means expressed as percentage of control values (SD). Comparison with control: $^{*}P < 0.05$; $^{**}P < 0.001$; $^{***}P < 0.001$.

10.5 (8.7–16.2), 35.6 (23.4–46.5) and 120.7 (95.8–135.8) µg and for C reflexes they were 4.3 (2.1–6.5), 14.2 (11.3–16.4) and 46.5 (35.7–54.3) µg respectively.

COMBINATION OF 1.5% SEVOFLURANE AND FENTANYL

The effect of sevoflurane was to cause a major increase in the effectiveness of fentanyl such that C and Aδ responses were completely abolished in all preparations by mean total doses of 32 µg and 64 µg of fentanyl respectively; Aδ and C reflexes returned to 38.2 % and 27% of control respectively 30 min after the withdrawal of sevoflurane and the remaining effect of fentanyl was subsequently reversed by naloxone (2 mg i.v.) (figs 3 and 4B). In the presence of 1.5% sevoflurane, $ED_{25,50,75}$ with 95% confidence intervals for fentanyl, calculated from the dose–response curves, for Aδ reflexes were 2.4 (1.3–3.3), 8.5 (6.3–10.9) and 30 (23.4–46.8) µg respectively, and the $ED_{50,75}$ for C reflexes were 3.7 (2.6–4.9) and 11.9 (11–19.5) µg respectively. These values were markedly less than those for intrathecal fentanyl alone, and showed a disproportionately larger increase in the effect of fentanyl in the presence of sevoflurane than would have been predicted from the sum of their effects.

If the effects of combinations of sevoflurane (1.5%) and intrathecal fentanyl on Aδ and C reflexes were additive, the theoretical predicted mean ED_{50} doses of fentanyl for Aδ and C reflexes would be 18 and 4.8 µg respectively instead of the observed values of 8.5 and 3.7 µg; also the predicted/observed dose ratios for the Aδ and C reflexes were 2.1 and 1.3 respectively. These observations indicate marked synergism between the two drugs, which is supported by the isobolograms shown in fig. 5.

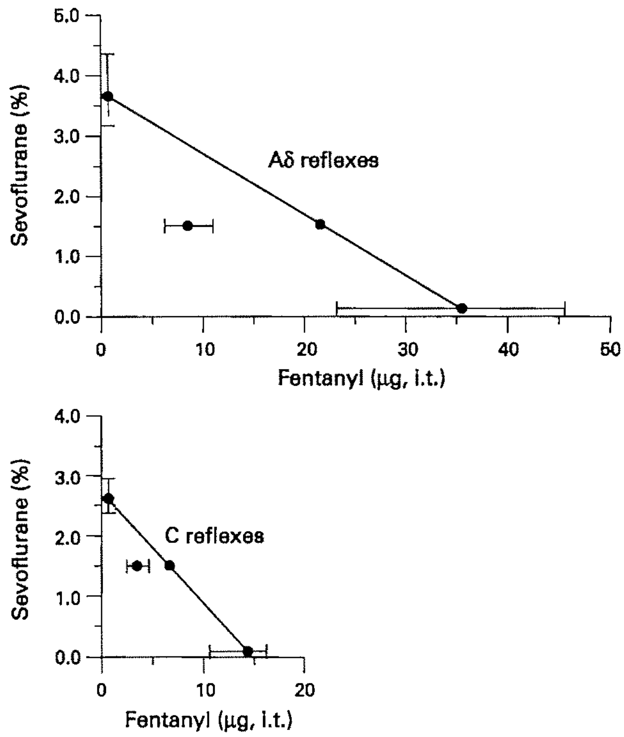

Figure 5 Isobolograms for sevoflurane coadministration with i.t. fentanyl in (A) Aδ-fibre-mediated and (B) C-fibre-mediated somatosympathetic reflexes evoked by supramaximal electrical stimulation of tibial nerves. The solid diagonal lines represent the additive line constructed by joining the ED_{50} (95% confidence intervals) dose of sevoflurane with that of fentanyl. The points on the lines (closed circles) are the predicted ED_{50} doses of fentanyl if its interactions with sevoflurane are additive. The points below the left of the diagonal line are the observed ED_{50} doses of fentanyl during sevoflurane administration. The horizontal lines are the 95% confidence intervals of the ED_{50} dose for fentanyl.

SPONTANEOUS SYMPATHETIC ACTIVITY

There were no significant changes in spontaneous sympathetic activity in any preparation throughout the present study, that is, with i.t. fentanyl, which abolished both Aδ and C reflexes, with sevoflurane alone in ED_{50} concentration for Aδ and C reflexes, and i.t. fentanyl used to abolish Aδ and C reflexes during the administration of 1.5% sevoflurane (figs 2 and 3).

RESTING HEART RATE AND MEAN ARTERIAL PRESSURE

Fentanyl

There were no significant changes in heart rate or MAP throughout the study.

Combination of 1.5% sevoflurane and fentanyl

Administration of 1.5% sevoflurane caused a decrease in mean heart rate from 168 beats min^{-1} (bpm) to 144 bpm (ns), after which there was no further reduction during the administration of fentanyl. The mean MAP was reduced from 120 mm Hg, that is the control level, to 98 mmHg (P <0.01) by 1.5% sevoflurane without any further reduction during the administration of i.t. fentanyl. Both mean heart rate and MAP returned to within control values 30 min after sevoflurane withdrawal, that is before the administration of naloxone (2 mg i.v.).

Discussion

This study shows for the first time that the combined antinociceptive effects of an inhalation anaesthetic agent and a spinally administered analgesic drug are not merely additive but highly interactive. It reveals the full extent of the synergistic interaction between the antinociceptive effects of sevoflurane and intrathecally administered fentanyl. It also confirms that sevoflurane, like fentanyl, has a greater effect on C compared with Aδ reflexes.[17]

The observation of the greater sensitivity of C-fibre responses to opioids is in keeping with previous work on morphine, fentanyl and alfentanil administered intrathecally,[18–20] which also applies to fentanyl, alfentanil, sufentanil and morphine when administered intravenously.[16 21–23] The ratio of the doses of i.t. fentanyl that depress Aδ and C reflexes, that is, 2.5:1, is of a similar order of magnitude to that for fentanyl during i.v. administration.[16]

Previous studies have shown that a reduction of the MAC of volatile agents is caused by opioids administered intrathecally or extradurally in both rats and humans.[11–14] For example, Drasner and colleagues reported that 0.75 mg morphine injected intrathecally in rats produced a 40% reduction in the MAC of halothane,[11] and more recent work has indicated that the extradural administration of morphine (4 mg) decreased the MAC of halothane by 28% in humans.[14] It has also been reported that the MAC of halothane is reduced in a dose-related manner by fentanyl administered extradurally in man.[13] The present study shows not only that sevoflurane causes a large augmentation of the effect of intrathecal fentanyl on Aδ- and C-fibre-mediated somatosympathetic reflexes but also that their interaction is highly synergistic.

Opioid receptors are found in the dorsal horn of the spinal cord on the terminals of small-diameter primary afferent fibres,[3–5] and it is well known that opioids, when administered intrathecally, depress nociceptive reflexes because of their actions in the dorsal horn area.[1 24 25] It has been suggested that in the spinal cord of the rat, which is the animal model most often used in experimental pain studies, 70% of the opioid receptor population are type μ, 24% are δ receptors and 6% are κ.[26] However, in the spinal cord of humans κ receptors are the predominant type at 50%, followed by μ, with 40%, with relatively fewer δ receptors.[27] The dog model used in the present study has a spinal cord length of comparable scale to that of the human, with an opioid-receptor distribution also similar to that in humans,[28] and is therefore a better model for clinically relevant experimental studies.

Interaction between the brain and spinal cord with respect to the action of inhalation agents has been the subject of a limited amount of work, summarized by Eger and colleagues.[10] The concentration required to produce amnesia and unconsciousness is approximately 25–40% of that needed to suppress purposeful movement.[6] Rampil and colleagues reported that in rats, decerebration does not decrease the anaesthetic concentrations required to produce immobility.[7 8] It has also been shown that if only supraspinal structures are exposed to inhalation anaesthetic agents, the concentrations required to produce anaesthesia and reflex depression are more than double those required in the normal situation when the spinal cord is also involved.[9] It would appear that the spinal cord is a principal site of action for inhalational anaesthetic agents.

Synergy between the actions of drugs depends on interactive pharmacodynamic effects, and these will clearly be influenced temporally by pharmacokinetics and spatially by functional interactions at different anatomic sites.[29] However, hitherto, there are no published reports on the type of pharmacodynamic interaction that occurs between an analgesic drug and an inhalation anaesthetic agent, such as fentanyl and sevoflurane.

At cellular level it has been demonstrated that opioid μ agonists increase potassium conductance in presynaptic neuronal membranes, causing membrane hyperpolarization and reduced excitability.[30] Opioids may reduce neuronal transmission by both inhibition of postsynaptic cell firing and through presynaptic reduction of neurotransmitter release.[31] Volatile anaesthetic agents reduce voltage-operated calcium currents in the central nervous system so as to cause a reduction in neurotransmitter release at presynaptic terminals.[32] It has also been shown that sevoflurane activates postsynaptic $GABA_A$ receptors in CA1 pyramidal neurons of rat hippocampus.[33] Therefore, sevoflurane and fentanyl may activate neurotransmitter systems, which may couple the same second-messenger system or G proteins[34] and therefore provide a basis for their synergistic interaction. However, for a single anaesthetic agent, the output of neuronal networks, modified by changes in the function of the cells within them, may show interactive amplification of effect to cause the anaesthetic state. The combined effects of anaesthetic and analgesic drugs will also reflect mechanisms fundamental to that state and any unified hypothesis of anaesthesia must embody the phenomenon of synergism.

Fentanyl, injected intrathecally in the lumbar region, depresses somatosympathetic responses evoked by stimulation of tibial nerves and recorded in renal nerves; this action occurs with no effect on spontaneous efferent sympathetic activity or responses to radial nerve stimulation, indicating that fentanyl's effects are localized to the afferent pathway.[19] This is true for other μ opioids unless there is significant systemic absorption, when there are effects on all afferent pathways and higher centres that regulate sympathetic activity.[20] For sevoflurane, it has been shown that compensatory baroreflexes, although depressed, retain sufficient activity at concentrations up to 3–4% to prevent effects on either spontaneous efferent sympathetic pathways or the heart rate.[35] Hence neither fentanyl nor sevoflurane would be expected to cause a reduction in spontaneous sympathetic activity, and this was confirmed for both drugs when administered alone and in combination throughout this study.

In conclusion, it has been shown that intrathecally administered fentanyl and inhaled sevoflurane interact with a high level of synergism to depress somatosympathetic reflexes. The dorsal horns of the spinal cord are likely to be a principal site for their interaction. In the concentration and doses used, either alone or in combination, they did not modify spontaneous sympathetic activity.

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Inhalation anaesthetics produce asynchronous reversal of ventilation inhomogeneity and increased lung resistance in a canine model of bronchial asthma

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Summary

Bronchial asthma is characterized by not only an increase in lung resistance but also inhomogeneous ventilation. We aimed to investigate how two inhalation anaesthetics, isoflurane and sevoflurane, relieve ventilation inhomogeneity and reduce lung resistance in the bronchoconstricted lung. We provoked bronchoconstriction in dogs by a continuous i.v. infusion of methacholine, then administered either isoflurane or sevoflurane. Ventilation inhomogeneity was quantified by the difference in respiratory phases between the regional alveolar pressures measured at two distinct lobes. We constructed a mathematical model that simulated our experimental results. Both anaesthetics decreased lung resistance ($P < 0.01$). Isoflurane significantly reduced the indices of inhomogeneity ($P < 0.01$). Sevoflurane exerted only a tendency to reduce uneven ventilation. Our model simulation suggested that the anaesthetics reduced ventilation inhomogeneity in preference to lung resistance when the dogs suffered from severe bronchoconstriction. (*Br. J. Anaesth.* 1998; **80**: 807–813)

Keywords: anaesthetics volatile isoflurane; anaesthetics volatile sevoflurane; lung mechanics; measurement techniques alveolar capsule; model mathematical; ventilation inhomogeneity

Some inhalation anaesthetics have potent bronchodilating actions and are used to treat status asthmaticus.[1 2] Bronchial asthma is characterized not only by increases in airflow resistance and lung elastance but also by uneven ventilation, which would lead to increased work of breathing.[3 4] These changes are produced by constriction of both airway and parenchymal tissues, and a heterogeneous distribution of the constricting tone across the lung.[5–7] Inhalation anaesthetics decrease lung resistance and elastance by several mechanisms including the direct relaxation of airway smooth muscle, inhibition of release of chemical mediators, and augmentation of β-adrenergic tone.[8–10] To our knowledge, however, no studies have focused upon the effect of inhalation anaesthetics on ventilation inhomogeneity.

In this study we questioned if inhalation anaesthetics would produce differential effects on lung resistance and ventilation inhomogeneity in the bronchoconstricted lung. We used the alveolar capsule technique and a two-compartment mathematical model to quantify ventilation inhomogeneity. The alveolar capsule technique measures regional alveolar pressures, and has shown direct evidence of substantial ventilation inhomogeneity in animal models of bronchial asthma.[11 13] The inhomogeneity can be expressed as the difference in respiratory phase between the regional alveolar pressures. The mathematical model was used to relate the phase difference to the discrepancy in regional respiratory time constants.

Methods

SURGICAL PREPARATION

After obtaining approval from the Ethics Committee of the Laboratory Animal Centre of our institute, we studied 21 healthy mongrel dogs weighing 12–28 kg. Anaesthesia was induced by an i.v. infusion of pentobarbital 25 mg kg^{-1}, and maintained with supplementary small doses of pentobarbital. A femoral vein was cannulated for fluid and drug administration. Tracheotomy was established and a cannula inserted into the trachea. The dogs were paralyzed with pancuronium bromide and ventilated with oxygen using a ventilator at a respiratory frequency of 12 breaths min^{-1}. A quasi-sinusoidal flow wave was generated by the ventilator at inspiration, and the dogs expired passively by the elastic recoil of lung tissue. The ratio of inspiratory to expiratory duration was one. After a median sternotomy, the chest was opened wide enough to expose as much lung surface as possible. A positive end-expiratory pressure of 0.5 kPa was applied to maintain a lung volume similar to the functional residual capacity of the intact animal.[14] Tidal volume was adjusted to maintain end-tidal carbon dioxide tension at approximately 5 kPa and kept constant throughout the experiment. Airway flow was measured at the trachea through a Fleisch 2 pneumotachograph connected to a differential pressure transducer.

Tracheal pressure (Ptr) was measured at the side port of the tracheal cannula by a pressure transducer. To measure the regional alveolar pressures (PA) at three different lobes we used the alveolar capsule technique, which has been described

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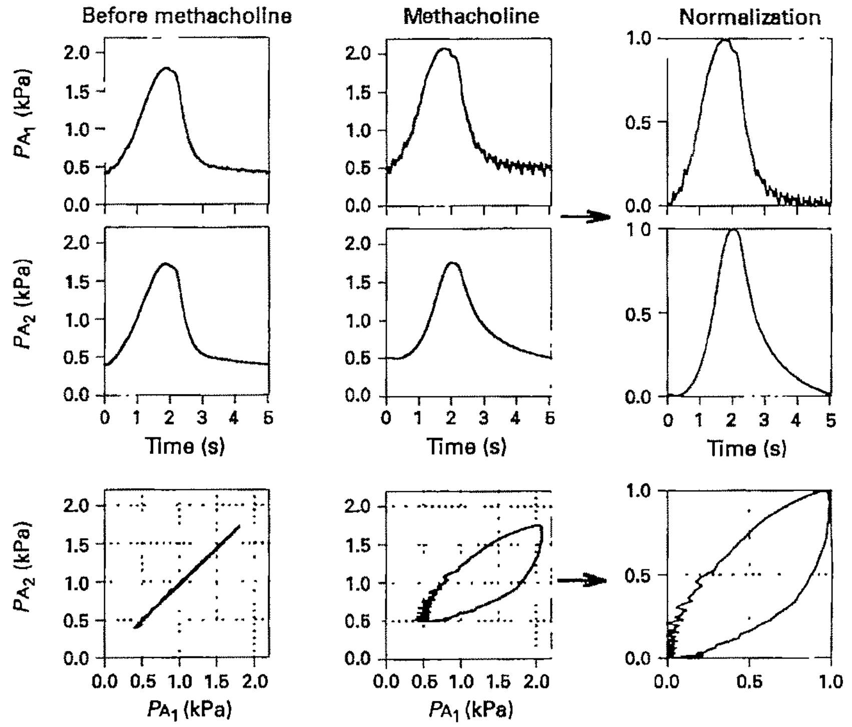

Figure 1 Alveolar capsule pressures and the area surrounded by the normalized alveolar pressures (A_{NOR}) in a representative dog. Left and centre columns represent the alveolar capsule pressures (P_{A_1} and P_{A_2}) in one breath before and after methacholine infusion, respectively. No looping is shown between PAs before methacholine, indicating homogeneous ventilation between the lung regions where PAs were measured. Clear looping is observed after methacholine, suggesting ventilation inhomogeneity between the lung regions. The right-hand column shows normalization of the respiratory amplitudes of PAs from the data shown in the centre column.

previously.[11-13 15-18] Briefly, three capsules (internal diameter 4 mm) were glued with cyanoacrylate on the parietal pleura of three different lobes. An electric cautery needle was used to make five to eight pinholes on the pleural surface inside the capsules, after which a miniature pressure transducer was plugged snugly into each capsule. This technique measured pressure in the alveoli just beneath the pleural surface. All signals were stored in a computer.

We continuously monitored the end-tidal carbon dioxide tension and anaesthetic concentration using an infrared respiratory gas analyser, and arterial blood pressure and heart rate via a catheter placed in the femoral artery.

EXPERIMENTAL PROCEDURE

After establishing stable circulatory and respiratory conditions, we started a continuous i.v. infusion of methacholine 0.25–0.5 mg kg^{-1} h^{-1}. The infusion rate was adjusted to obtain noticeable ventilation inhomogeneity. This level of inhomogeneity was defined as that at which clear looping was observed between any of two PA but no PA indicated the closure of the airway to which the alveoli led. When a PA did not show the pressure swing that synchronized with the breathing cycle, we considered the airway closed. Once the infusion rate was established, it was kept constant throughout the period of data acquisition.

We divided the 21 dogs into three groups. Seven dogs in the baseline group were challenged solely with methacholine, and measured continuously for the same duration as the inhalation groups. The remaining 14 dogs were allocated to two groups;

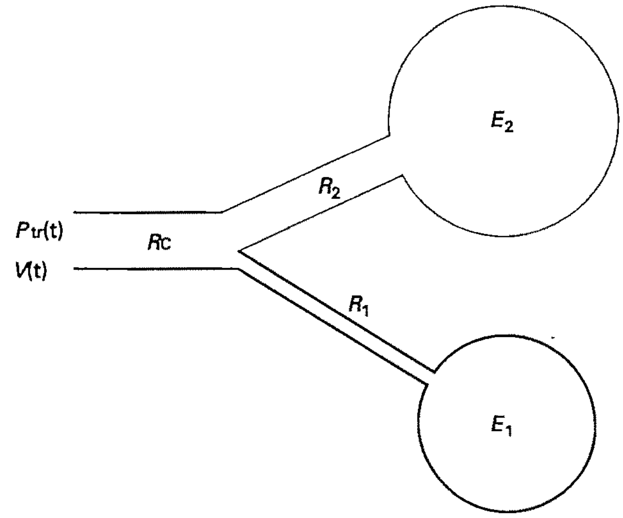

Figure 2 Parallel two-compartment model. The model consists of two compartments connected in parallel to each other at an end of a common airway (Rc). Each compartment comprises a single airway (R_L, L = 1, 2) leading to a single alveolus (E_L). Rc, R_L, and E_L denote common airway resistance, compartmental resistance and elastance, respectively. Ptr(t) and V(t) indicate the pressure applied at the trachea and the ventilation volume.

after induction of bronchoconstriction one group inhaled isoflurane and the other sevoflurane. We used in succession three concentrations of inspired anaesthetic (0.5, 1.0, and 1.5 MAC), as follows. After stable bronchoconstriction was established, we carried out a total lung capacity (TLC) manoeuvre (three consecutive lung inflations each to a volume approximately twice as large as the tidal volume) to avoid atelectasis. The TLC manoeuvre produced transient decreases in Ptr and PA. When pressure

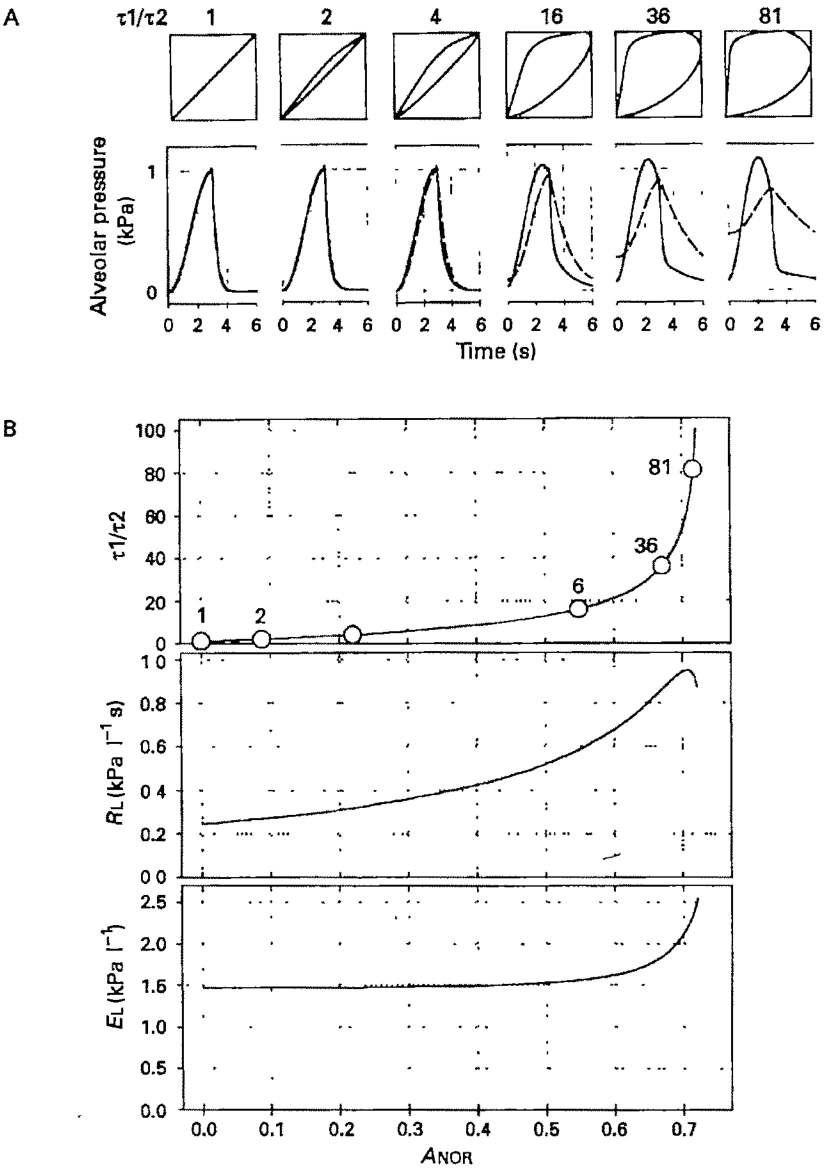

Figure 3 Results of the simulation study. Data are presented as measured variables.
(A) Looping in the normalized P_A–P_A plots at various values for $\tau 1/\tau 2$ (upper panels) and alveolar pressures of the two compartments in a single breath (lower panels).
(B) Behaviours of $\tau 1/\tau 2$, R_L, and E_L with change in A_{NOR}. Open circles in the plot of $\tau 1/\tau 2$ indicate the points at $\tau 1/\tau 2$ of 1, 2, 4, 16, 36, and 81, respectively. $\tau 1/\tau 2$ exhibited a relationship with A_{NOR}: $\tau 1/\tau 2 = -\ln((0.708 - A_{NOR})/0.741)$. We used this relationship to calculate $\tau 1/\tau 2$ from A_{NOR}.

signals were stable after these transient decreases, we administered isoflurane or sevoflurane with an end-expiratory concentration equivalent to 0.5 MAC while measuring continuously for 5 min. The TLC manoeuvre was reapplied, anaesthetic concentration increased to 1 MAC, and measurement performed for another 5 min, and then the procedure repeated using an anaesthetic concentration of 1.5 MAC.

Concentrations of MAC for isoflurane and sevoflurane in dogs were 1.4% and 2.4%, respectively.[19]

DATA ANALYSIS

The volume signal (V) was obtained by numerical integration of the flow ($\dot{V}$) signal. We determined resistance and elastance of the global lung on a breath-to-breath basis. Data were segmented into consecutive single breath signals at end-expiratory points. Using a multiple least-squared linear regression, each single breath datum was fitted to a single-compartment model of the lung, according to the equation:

$$P_{TR} = R_L\dot{V} + E_L V + K$$

where R_L and E_L denote lung resistance and elastance, respectively, and K represents the end-expiratory pressure. This fitting procedure allowed us to observe breath-wise trends in the lung mechanical parameters.[20]

Uneven ventilation produced a difference in respiratory phases between regional alveolar pressures (P_A), creating a loop in the plot of two P_As. We used the area of the loop as an index of ventilation inhomogeneity. The loop area was affected by both the amplitudes of P_As in a breathing cycle and the difference in regional respiratory phases between P_As, although the amplitude itself does not imply inhomogeneity. We therefore

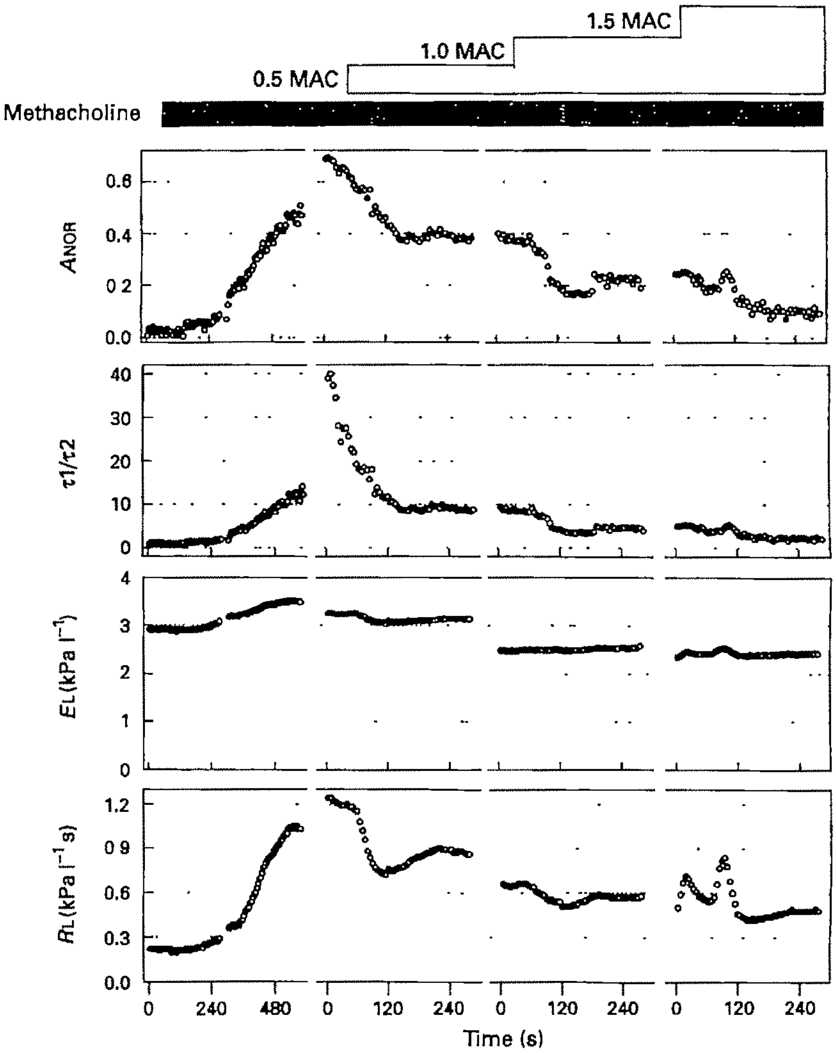

Figure 4 Sequential changes in *A*NOR, $\tau 1/\tau 2$, *E*L, and *R*L in a representative dog that inhaled isoflurane. Data are presented as measured variables.

normalized the amplitudes of *P*AS in a breath cycle to one. Thus we considered that the area enclosed by the two normalized *P*AS (*A*NOR) could represent purely ventilation inhomogeneity between the two lung regions (fig. 1).

After administration of methacholine, *P*AS sometimes exhibited time–signal curves that indicated closure of the airways leading to the alveoli where *P*A was measured, presumably because of severe small-airway constriction and mucous plugging (menisci). In this study, therefore, we used only *P*A signals measured at the alveoli whose parent airways we considered to be maintained open. Further, we discarded results from dogs that did not have at least two *P*AS measured at "open-airway alveolar regions" throughout the experiment.

QUANTITATIVE EVALUATION OF VENTILATION INHOMOGENEITY USING A MODEL SIMULATION

The parameter *A*NOR permits only quasi-quantitative evaluation of ventilation inhomogeneity. For example, doubling *A*NOR does not necessarily mean doubling the inhomogeneity. In an attempt to assess the inhomogeneity in a more quantitative manner, we adopted a two-compartment model (fig. 2). The model consists of two compartments connected in parallel at one end of a common airway, with each compartment comprising a single airway leading to a single alveolus. The model is described in detail elsewhere.[21 22] A factor indicating the relative ventilation of each compartment is the respiratory time constant (τ = resistance/elastance), and when time constants differ between two compartments, inhomogeneous ventilation and looping in the plot of the alveolar pressure signals are observed. We defined the ratio of the two time constants ($\tau 1/\tau 2$) as an index of ventilation inhomogeneity. When $\tau 1/\tau 2$ is 2, for example, the change in ventilatory volume of compartment one is twice as slow as that in compartment two. We determined the relationship between $\tau 1/\tau 2$ and *A*NOR by changing the values of model parameters in simulating mechanical ventilation of the two-compartment model. In the model simulation, we produced ventilation inhomogeneity, that is, a difference in time constants, by changing compartmental resistances, R_1 and R_2, while keeping compartmental elastances, E_1 and E_2, constant. Ventilatory conditions were similar to those used in the dog experiments.

STATISTICAL ANALYSIS

For between- and within-group comparisons, the averages of the parameter values of the last six

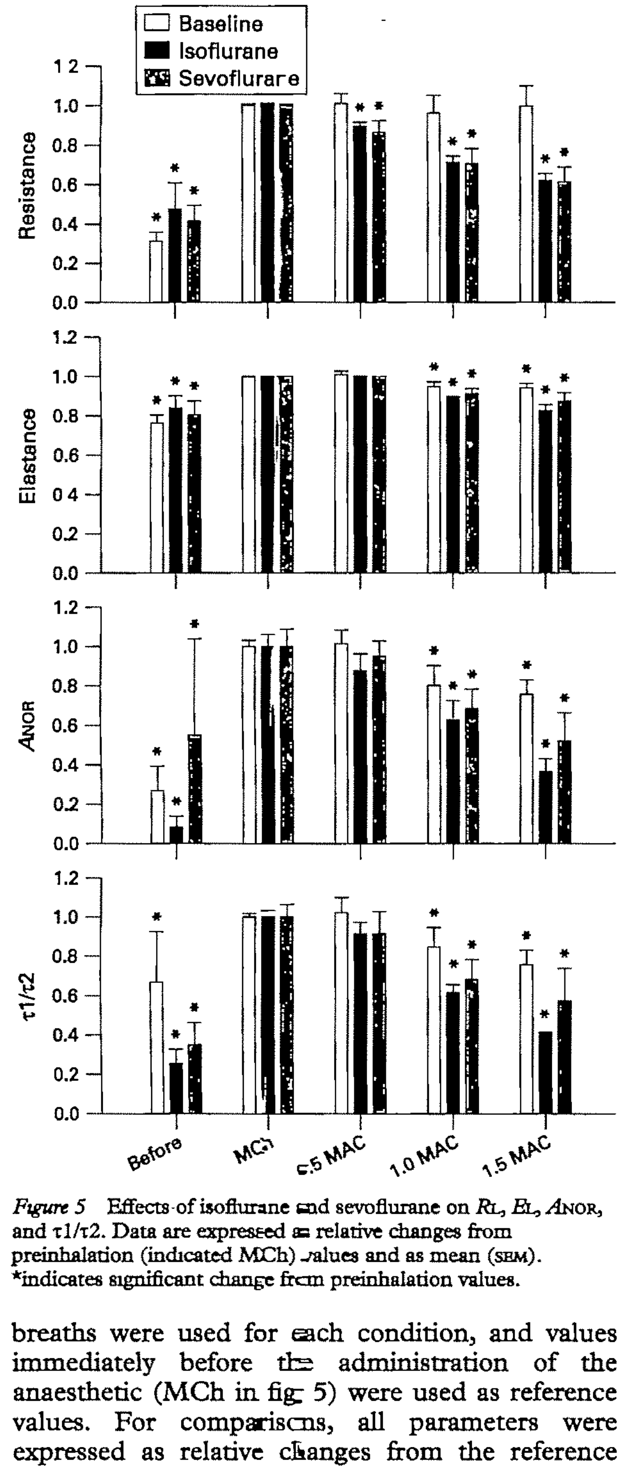

Figure 5 Effects of isoflurane and sevoflurane on *R*L, *E*L, *A*NOR, and $\tau 1/\tau 2$. Data are expressed as relative changes from preinhalation (indicated MCh) values and as mean (SEM). *indicates significant change from preinhalation values.

breaths were used for each condition, and values immediately before the administration of the anaesthetic (MCh in fig. 5) were used as reference values. For comparisons, all parameters were expressed as relative changes from the reference values. A multivariate analysis of variance followed by a contrast analysis was performed to examine differences between any particular parts of the design. $P < 0.05$ was considered significant. Statistical power ($1 - \beta$) was estimated, when the null hypothesis was accepted for between-group comparisons.

Results

Results of the simulation are shown in fig. 3. The model simulated the looping presented in *P*A-*P*A plots in dogs (upper panels in fig. 3A), and $\tau 1/\tau 2$ was observed to increase with increasing *A*NOR. As shown in the lower panels of fig. 3A, *P*As were superimposed completely on each other when the two compartments ventilated homogeneously ($\tau 1=\tau 2$). However, as ventilation inhomogeneity progressed with increasing $\tau 1/\tau 2$ ratio, the disagreement between two *P*As widened in both phase and magnitude.

Figure 3B shows the behaviours of $\tau 1/\tau 2$, *R*L, and *E*L with change in ANOR. All parameters presented exponential increases with increasing ANOR. $\tau 1/\tau 2$ revealed a slower increase at low *A*NOR whereas a more rapid increase at high ANOR than *R*L or *E*L. On the other hand, *R*L presented a more uniform increase than $\tau 1/\tau 2$. These results indicate that a greater change occurs in ventilation inhomogeneity ($\tau 1/\tau 2$) than in *R*L when *A*NOR is large. When *A*NOR exceeded 0.7, *R*L presented as a decrease. *E*L increased as inhomogeneity developed regardless of the constant compartment elastances.

Figure 4 shows sequential changes in parameters, *A*NOR, $\tau 1/\tau 2$, *R*L, and *E*L, in a representative dog that inhaled isoflurane. Both *R*L and *E*L presented as relatively smooth trends, while both *A*NOR and $\tau 1/\tau 2$ exhibited greater between-breath variability.

Figure 5 and table 1 summarize the effects of two anaesthetic agents on *R*L, *E*L, *A*NOR, and $\tau 1/\tau 2$. As for the within-group change (fig. 5), both isoflurane and sevoflurane decreased all parameters significantly from the preinhalation (indicated as MCh) values in a dose-dependent manner. In the baseline group, *E*L, *A*NOR, and $\tau 1/\tau 2$ decreased in a time-dependent manner, while *R*L remained unchanged during the methacholine infusion. Table 1 summarizes the results of inter-group comparisons. Compared with the baseline group, both isoflurane and sevoflurane reduced *R*L, indicated by both significant main effects and interactions. Isoflurane significantly reduced *A*NOR and $\tau 1/\tau 2$, whereas sevoflurane produced only a tendency to reduce the inhomogeneity indices ($P = 0.262$ for *A*NOR and $P = 0.341$ for $\tau 1/\tau 2$). A statistical power analysis

Table 1 Summary of between-group statistical comparisons. NS, not significant. Values in the parentheses after NS indicate estimated statistical power, $1-\beta$. For simplicity, only comparisons between the baseline *v* either inhalation group are given

		Main effects (*v* baseline)	Interactions (*v* baseline)	Comparison with the baseline group at each concentration		
				0.5 MAC	1.0 MAC	1.5 MAC
Lung resistance	Isoflurane	P=0.020	P<0.001	NS	P=0.041	P=0.010
	Sevoflurane	P=0.041	P=0.002	NS	NS	P=0.017
Lung elastance	Isoflurane	P=0.037	P=0.010	NS	NS	P=0.024
	Sevoflurane	NS (0.096)	NS (0.092)	NS	NS	NS
ANOR	Isoflurane	P=0.029	P=0.011	NS	NS	P<0.001
	Sevoflurane	NS (0.084)	NS (0.080)	NS	NS	NS
$\tau 1/\tau 2$	Isoflurane	P=0.040	P=0.035	NS	NS	P=0.0059
	Sevoflurane	NS (0.050)	NS (0.050)	NS	NS	NS

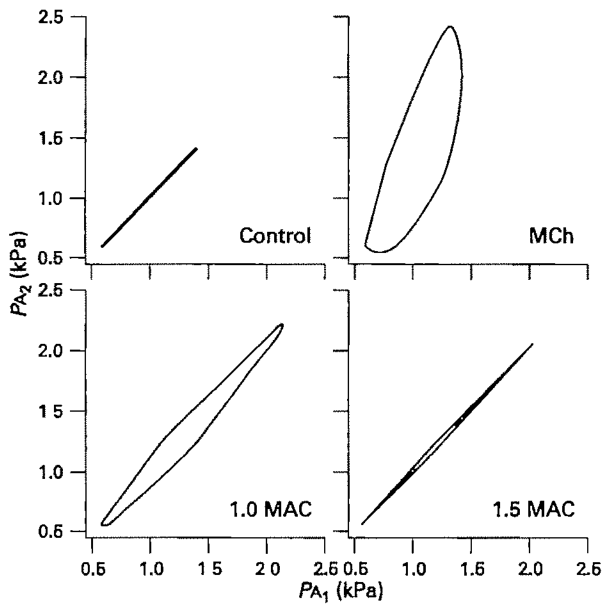

Figure 6 An example of the differential effects of the inhalation anaesthetics on lung constricting tone and ventilation inhomogeneity. Data are shown as measured variables. The dog inhaled sevoflurane after bronchoconstriction produced by methacholine. Control, before methacholine infusion; MCh, methacholine infusion before sevoflurane inhalation. 1.0 MAC and 1.5 MAC, sevoflurane inhalation at 1.0 and 1.5 MAC after methacholine infusion.

performed between sevoflurane and baseline groups resulted in a poor statistical power, 1 – β, of less than 0.1.

Discussion

This study is, to our knowledge, the first to present direct evidence that isoflurane reduces ventilation inhomogeneity in an animal model of bronchial asthma. The reduction in uneven ventilation may be an expected result, as both increased lung resistance and ventilation inhomogeneity may be produced by the same lung-constricting process, induced by methacholine and then reversed by isoflurane.

According to our simulation, however, the inhalation anaesthetics might reduce ventilation inhomogeneity and lung resistance in an asynchronous manner. The difference in the exponential curvature between τ1/τ2 and *R*L (fig. 3B) indicates that the amount of change in inhomogeneous ventilation was greater than that in *R*L when the animals exhibited severe bronchoconstriction. For example, a reduction of *A*NOR from 0.7 to 0.5 implies a 72% decrease in τ1/τ2 (48.7 to 13.7), whereas *R*L decreased by only 45% (9.6 to 5.3). These findings suggest that the inhalation anaesthetics have a greater differential effect on ventilation inhomogeneity and lung resistance when the lung exhibits more severe bronchoconstriction, and thus greater inhomogeneity and lung resistance.

Supportive evidence is presented in fig. 4. In the dog, isoflurane at 0.5 MAC produced a 25% (1.2 to 0.9 kPa l^{-1} s) decrease in *R*L, while reductions in *A*NOR and τ1/τ2 amounted to 43% (0.7 to 0.4) and as much as 75% (40 to 10), respectively. Figure 6 shows another example indicating the differential effects of inhalation anaesthetic agents. The figure presents plots of a *P*A *vs* another *P*A of a single breath in various conditions in a single dog. The area of the loop was significantly reduced after inhalation of isoflurane, while the respiratory amplitudes of *P*As were relatively unchanged. This suggests that isoflurane preferentially reduced the inter-regional inhomogeneity rather than the constricting tone of the global lung.

The two-compartment model may oversimplify our experimental results, because the ventilation inhomogeneity should have been distributed across most of the lung regions.[11 21 22] However, Sato and colleagues described a mathematical model in which substitution of a few alveolar pressures gave a good quantitative representation of the mechanical behaviour of the lung in an animal model of bronchial asthma.[12 23] We believe, therefore, that the asynchronous reversal in inhomogeneous ventilation and lung resistance was not produced spuriously through our model simulation.

Several studies have shown both temporal and spatial variation in the constricting response of regional tissues.[24 25] Inhalation anaesthetic agents have shown the topographical difference in relaxing airways and lung parenchyma.[7 26] These findings could be related to the asynchronous recovery observed in our study. Inhalation anaesthetics may homogenize constricting tone (both resistive and elastic) of regional lung tissues before reducing the global lung tone when severe constriction is exhibited. This would lead to homogeneous redistribution of regional ventilatory time constants even if the lung resistance of the global lung remains increased.

Reduction of ventilation inhomogeneity may decrease wasted ventilation. This would be beneficial to gas exchange in the lung, even if the global lung resistance remains unchanged.

Sevoflurane produced only a tendency to reduce uneven ventilation. We consider, however, that no essential difference exists between sevoflurane and isoflurane, because: (1) there was no statistical difference between the two agents in their effects on *A*NOR, τ1/τ2, *R*L and *E*L; and (2) the result of our statistical power analysis indicated that a relatively small number of subjects could account for a failure to detect differences between baseline and sevoflurane groups.[27]

In summary, we have investigated how isoflurane and sevoflurane decrease inhomogeneous ventilation and raised lung resistance in a canine model of bronchial asthma induced by methacholine. The anaesthetic agents produced asynchronous recoveries from ventilation inhomogeneity and increased lung resistance.

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Effects of nalbuphine, pentazocine and U50488H on gastric emptying and gastrointestinal transit in the rat†

T. ASAI, W. W. MAPLESON, I. POWER

Summary

We studied the effect of mixed agonist–antagonist opioids (nalbuphine and pentazocine) and a kappa opioid agonist (U50488H) on gastric emptying and gastrointestinal transit, and their interactions with morphine in rats. In each group, nalbuphine (0.01–30 mg kg^{-1}), pentazocine (1–30 mg kg^{-1}), U50488H (1–100 mg kg^{-1}1) or saline was injected i.p. at 0 min. Another four groups of rats received morphine 13.4 mg kg^{-1} (ED75) and one of the following substances: saline, nalbuphine, pentazocine or U50488H. In both groups, at 30 min, radiolabelled saline 1 ml was infused into the stomach; at 1 h, gastric emptying and gastrointestinal transit were calculated by measuring the radioactivity in the gastrointestinal tract. Slopes for dose–response curves were determined. Nalbuphine significantly, but only weakly, delayed gastric emptying ($P < 0.0005$) and gastrointestinal transit ($P < 0.01$). Pentazocine markedly inhibited both, whereas U50488H did not significantly inhibit either. The slopes of the dose–response curves for nalbuphine, but not for pentazocine, on both gastric emptying and gastrointestinal transit were significantly less steep than those for morphine. Nalbuphine significantly antagonized the inhibitory effect of morphine on gastric emptying ($P = 0.005$) and gastrointestinal transit ($P = 0.02$), whereas pentazocine and U50488H did not. Nalbuphine and pentazocine delay gastric emptying and gastrointestinal transit, possibly by different mechanisms. (*Br. J. Anaesth.* 1998; **80**: 814–819)

Keywords: interactions (drug) opioids; gastrointestinal tract gastric emptying; complications gastric statis; rat

Opioids may bind to more than one receptor, and the intrinsic activity for each receptor may differ.[1] Some of them have no or weak intrinsic activities to produce agonist effects at one receptor (competitive or partial agonists). When a partial agonist and a full agonist are given concurrently, binding of the full agonist will be partially prevented by binding of the partial agonist, and thus the effect of the full agonist will be reduced. For example, the opioid nalbuphine antagonizes the antinociceptive effect of mu opioid receptor agonists.[2] Such opioids are called mixed agonist–antagonist opioids, and include nalbuphine, nalorphine and pentazocine.[1 3]

Mu opioid receptor agonists, such as morphine, delay gastric emptying and intestinal transit.[4–6] In contrast, kappa receptor opioid agonists have weak or no inhibitory effects.[4 5] Little is known about the effects and mechanisms of mixed agonist–antagonist opioids on gastric emptying and intestinal transit. In mice, nalbuphine, nalorphine and pentazocine delayed gastrointestinal transit, but the inhibitory effect was weak.[7–9] We found only one report in which the effect of the mixed agonist–antagonist on gastric emptying was studied in animals.[10] In that study, the residual volume of gastric contents was examined 30 min after infusion of dyed antacid into the stomach and injection of either pentazocine or saline in rats. The residual volume was greater in the pentazocine group than the saline group; however, the residual volume in the pentazocine group was greater than the volume of initial infusion of dyed antacid. Antacid itself delays gastric emptying and increases gastric acid secretion[11 12]; therefore, the effects of pentazocine are not clear.

More than one opioid, such as nalbuphine and morphine, may be given concurrently during surgery.[13 14] The interactive effects of these drugs and the effect on gastrointestinal motility are not known.

We decided to study the effects of a mu agonist (morphine), mixed agonist–antagonists (nalbuphine and pentazocine) and a highly selective kappa agonist (U50488H) on gastric emptying and gastrointestinal transit; we also studied the interactive effects of these opioids.

Materials and methods

The study was conducted under the Animal (Scientific Procedures) Act 1986 (Home Office Licence: PPL 40/954, PPL 40/1397). Male Wistar rats, each weighing 200–250 g, were housed under standard controlled environmental conditions, with a 12 h light–dark cycle. The animals were fasted for 24 h, but allowed free access to water until 20–30 min before the start of the experiment. They were kept in individual wire-mesh cages to prevent coprophagy

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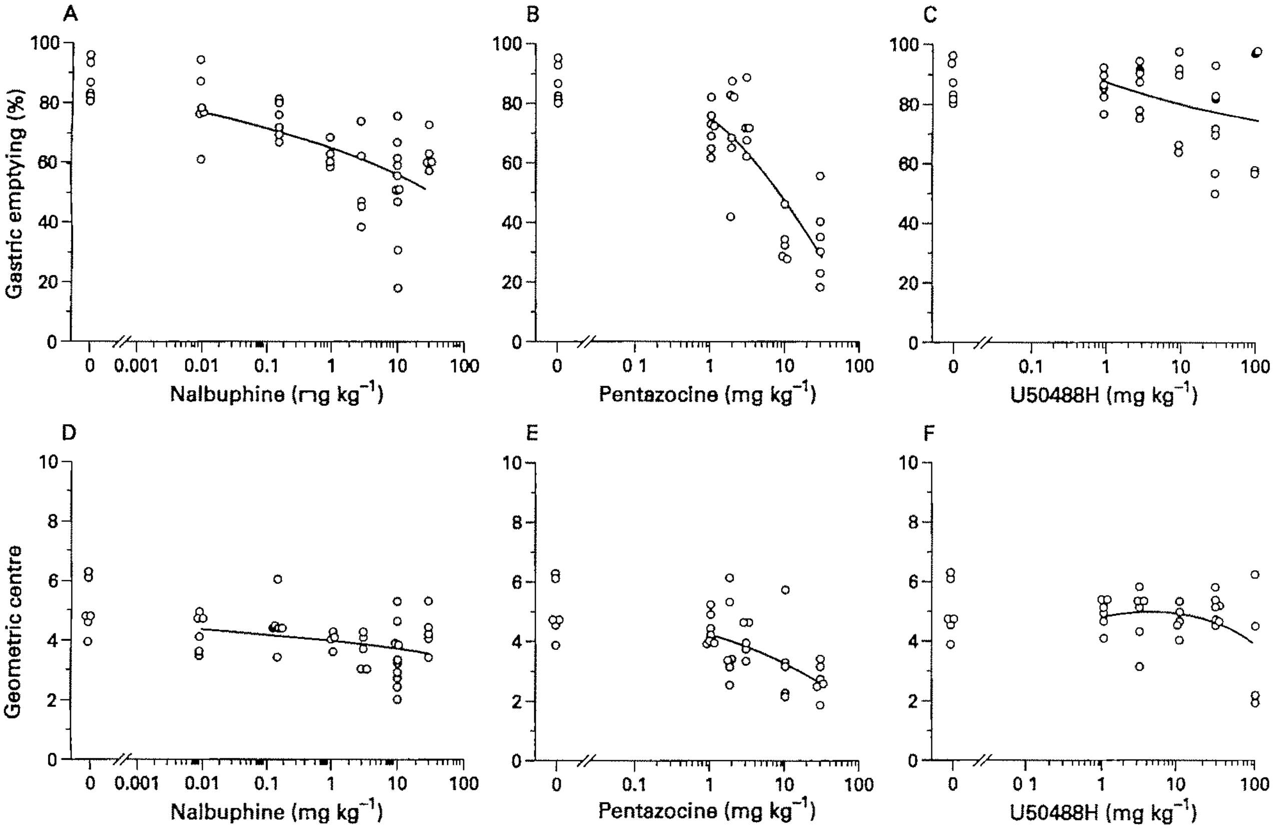

Figure 1 Effect of nalbuphine (A, D), pentazocine (B, E) and U50488H (C, F) on gastric emptying and gastrointestinal transit of saline. Note the narrow range of doses for pentazocine and U50488H. Saline 1 ml, containing a radiolabelled marker (^{51}Cr), was given 30 min after i.p. injection of the drug. Gastric emptying and gastrointestinal transit were examined 30 min later. A fitted logit dose–response curve (nalphine or pentazocine) or a fitted parabola (U50488H) is shown, with the value obtained from each rat (open circles). Symbols are slightly displaced if there are similar values for any given dose. Values at zero dose are those for the saline control.

during fasting. All experiments were started between 10:00 and 11:00. Nalbuphine, pentazocine (Sigma Chemical Co., UK) and U50488H (Upjohn Company, USA) were prepared freshly on each day of the experiment.

A group of six rats was allocated for each set of circumstances. If more than one rat was excluded, another group of six rats was used until a group was completed in which no more than one rat was excluded. Data from the non-excluded rats from all groups for each study (5–10 rats) were used.

Gastric emptying and gastrointestinal transit were studied, as described previously.[15] In brief, at 0 min, a substance or a combination of substances (see below), in a volume of 1.0 ml kg^{-1} for each substance was given i.p. At 30 min, 1.0 ml of saline containing radiolabelled sodium chromate was infused into the stomach. At 60 min, the rats were killed. The stomach and small intestine were removed, and the small intestine divided into 10 equal segments. The radioactivity in the stomach and each segment of the intestine was counted. If there was chyme in the stomach or small intestine, the data were not used.

Table 1 ED_{50} (mg kg^{-1}) (95% confidence limits) of opioids injected intraperitoneally in inhibiting gastric emptying and gastrointestinal transit of 1 ml saline. The estimated values and their upper confidence limits are omitted when the values are much greater than the dose range used. *Data for morphine are from a previous report.[8] †U50488H up to 100 mg kg^{-1} did not significantly delay gastric emptying and gastrointestinal transit

Drugs	Gastric emptying	Gastrointestinal transit
Morphine (*n*=52)*	2.8 (2.1, 3.8)	1.2 (0.87, 1.71)
Nalbuphine (*n*=36)	— (28.1, —)	— (369, —)
Pentazocine (*n*=29)	12.8 (8.2, 24.7)	39.8 (16.0, —)
U50488H (*n*=28)	—†	—†

Gastric emptying and gastrointestinal transit (expressed in terms of the geometric centre) in each rat and the percentage inhibition of gastric emptying or gastrointestinal transit for each test drug were calculated.[15]

EFFECTS OF INDIVIDUAL OPIOID AGONIST

We studied the effects on gastrointestinal motility of three different types of opioid receptor agonist: a mu opioid receptor agonist (morphine, 0.1–30 mg kg^{-1}); a

Table 2 Slopes (logit (% gastric emptying) or logit (% geometric centre) per unit log dose) and differences in slopes of the logit curves (with 95% confidence limits (CL)) for the effect of opioids on gastric emptying and gastrointestinal transit of saline

Drugs	Slopes (95% CL)	*P*
Gastric emptying		
Morphine (*n*=52)	−1.38 (−1 48, −1.29)	
Nalbuphine (*n*=36)	−0.48 (−0 55, −0 40)	
Pentazocine (*n*=29)	−1.67 (−1.8, −1 5)	
Differences between drugs		
Morphine — nalbuphine	−0.91 (−1.27, −0.55)	<<0 001
Morphine — pentazocine	0.29 (−0.28, 0.86)	0 32
Gastrointestinal transit		
Morphine (*n*=52)	−0.97 (−1.05, −0 89)	
Nalbuphine (*n*=36)	−0.23 (−0.30, −0.16)	
Pentazocine (*n*=29)	−1.03 (−1.18, −0 88)	
Differences between drugs		
Morphine — nalbuphine	−0.74 (−1.05, −0.44)	<<0.001
Morphine — pentazocine	0.06 (−0.43, 0.54)	0.82

Table 3 Effect of nalbuphine, pentazocine or U50488H on the inhibitory effect of morphine on gastric emptying and gastrointestinal transit of saline (median). Non-parametric one-way analysis of variance (Kruskal–Wallis test) showed a significant difference in gastric emptying ($P<0.05$) and gastrointestinal transit ($P=0.01$) between groups; the Minitab version of Mann–Whitney *U* test was used to obtain *P* values and 95% confidence limits of the difference between rats that received morphine with saline and those that received a combination of morphine and an agonist. Six to seven rats were used for each group

	Gastric emptying			Gastrointestinal transit		
		Difference from morphine group			Difference from morphine group	
Treatment	Emptying (%)	Confidence limits	*P*	Geometric centre	Confidence limits	*P*
Morphine 13.4 mg kg^{-1}						
+ saline	20.0			1.4		
+ nalbuphine 1.0 mg kg^{-1}	41.0	(4.0, 32.2)	0.02	3.1	(0.4, 2.1)	0.005
+ pentazocine 1.0 mg kg^{-1}	22.5	(−8.0, 11.0)	0.41	1.5	(−0.4, 0.9)	0.65
+ U50488H 1.0 mg kg^{-1}	22.1	(−9.8, 19.3)	0.41	1.6	(−0.4, 0.8)	0.47

kappa opioid receptor agonist (U50488H, 1–100 mg kg^{-1})[16]; and a mixed agonist–antagonist opioid (nalbuphine, 0.01–30 mg kg^{-1}, and pentazocine, 1–30 mg kg^{-1}). However, only four rats were used for 100 mg kg^{-1} U50488H, because of limited availability of the drug. Data for morphine have been reported already,[15] but were not used in any hypothesis tests. The experiments with the other three opioids were all conducted within the period over which the measurements with morphine were made.

INTERACTIONS OF TWO OPIOID AGONISTS

Another four groups of rats received morphine 13.4 mg kg^{-1} (ED$_{75}$) and one of the following substances: saline, nalbuphine, pentazocine or U50488H (the last three at 1.0 mg kg^{-1}).

STATISTICAL ANALYSIS

The variation of percentage inhibition with the dose of each agent was modelled, except for results for U50488H, by fitting a sigmoid logit curve to fractional inhibition against log dose, to calculate ED$_{50}$ and ED$_{75}$ and, by means of the Fieller equation, the 95% confidence interval (CI) of those doses.[15]

When the logit curve showed that the test drug did not inhibit gastric emptying or gastrointestinal transit by more than 50%, the Mann–Whitney *U* test was used to compare gastric emptying and gastrointestinal transit between the drug and saline groups of rats; the values for all doses of the test drug were pooled for this analysis. $P < 0.05$ was considered significant.

For U50488H, it was not legitimate to fit a logit curve because of many negative values for percentage inhibition. Therefore, to see if there was any tendency for inhibition to increase with increasing dose, a linear and a quadratic equation were fitted to the data and tested for significant negative slope and negative curvature, respectively.

The 95% confidence intervals for median difference between saline and drug groups were calculated using the SINTERVAL command (sign test) in Minitab Release 8.2 (running on a Macintosh LC computer), which shows exact intervals for a stated confidence level close to 95%.

The slope of each logit curve and the difference between the slopes for two drugs (e.g. morphine and nalbuphine), and the standard errors, emerge from the GLIM analysis. The 95% confidence intervals for the slopes and differences of slopes were calculated as described by Gardner and Altman.[17]

To study the interactive effects of morphine and an agonist (nalbuphine, pentazocine or U50488H), non-parametric one-way analysis of variance (Kruskal–Wallis test) was used to compare gastric emptying and gastrointestinal transit between the four groups. If this proved significant, the Mann–Whitney *U* test was used to compare gastric emptying and gastrointestinal transit between rats that were subjected to morphine (and saline), and those that received a combination of morphine and another agonist (nalbuphine, pentazocine or U50488H).

Results

EFFECTS OF INDIVIDUAL OPIOID AGONIST

Nalbuphine significantly delayed gastric emptying ($P < 0.0005$ by Mann–Whitney *U* test), but its inhibitory effect was weak (95% CI for the difference from saline: 15.1–35.9% at the maximum dose of nalbuphine, 30 mg kg^{-1}) (fig.1; table 1). It also significantly decreased gastrointestinal transit ($P < 0.01$), but its inhibitory effect was weak (95% CI for difference from saline: − 0.5 – − 2.2% at the maximum dose, 30 mg kg^{-1}) (fig.1).

Pentazocine significantly delayed both gastric emptying and gastrointestinal transit (fig.1; table 1).

U50488H did not significantly inhibit either gastric emptying or gastrointestinal transit. The Mann–Whitney *U* test showed no significant difference in either gastric emptying and gastrointestinal transit between U50488 and saline groups (table 1), and neither the slope of a fitted straight line nor the curvature of a fitted parabola was significant (fig.1).

The slopes of the dose–response curves for nalbuphine on both gastric emptying and gastrointestinal transit were significantly less steep than those for morphine ($P << 0.001$) (table 2). In contrast, the slopes for pentazocine were similar to those for morphine (table 2).

INTERACTIVE EFFECTS OF TWO OPIOID AGONISTS

One-way analysis of variance showed that the values were significantly different between the four groups, for gastric emptying ($P < 0.05$) and gastrointestinal transit ($P = 0.01$) (table 3). Nalbuphine significantly antagonized the inhibitory effect of morphine on

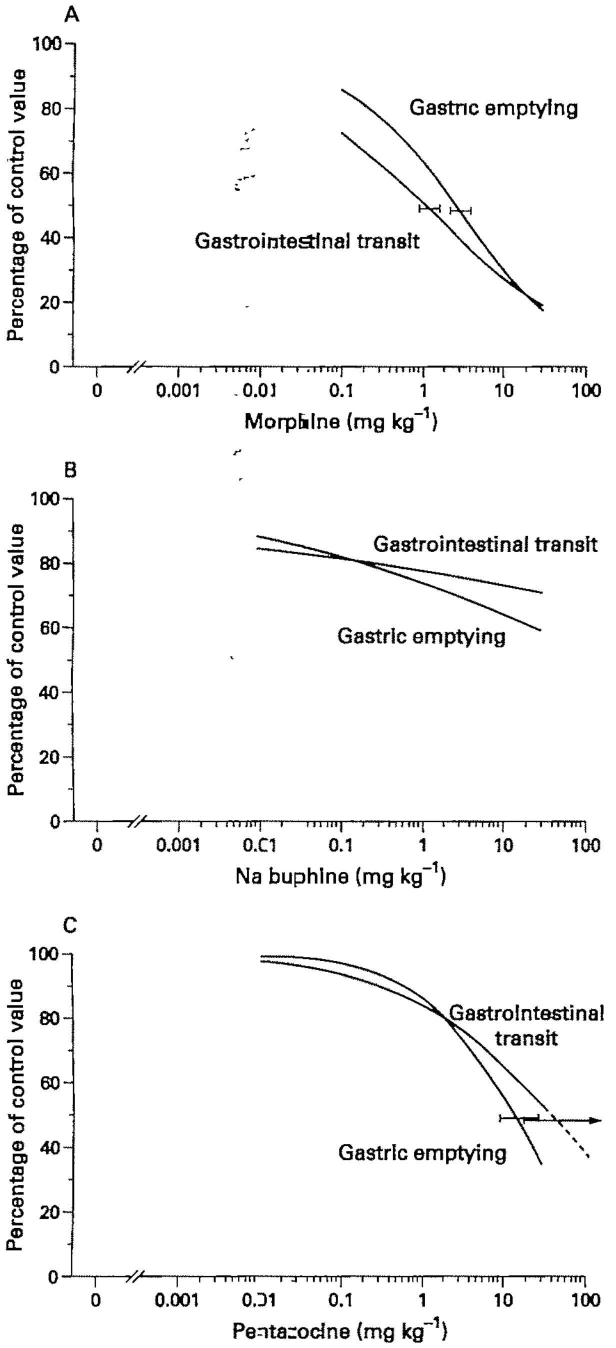

Figure 2 Gastric emptying and gastrointestinal transit as percentages of the control values for (A) morphine, (B) nalbuphine and (C) pentazocine. The extrapolated part of the curve for pentazocine is shown by a broken line. ED_{50} values and 95% confidence intervals are also shown. Data for morphine are from a previous study.[8]

gastric emptying (P = 0.02) and gastrointestinal transit (P = 0.005), whereas pentazocine and U50488H did not (table 3).

Discussion

Nalbuphine and pentazocine significantly inhibited gastric emptying and gastrointestinal transit of saline, but the effects were weak for nalbuphine. These findings are consistent with previous reports, which have shown that nalbuphine and pentazocine have weak inhibitory effects on transit in the small intestine in mice.[7–9] In contrast, in accordance with previous reports in rats and mice,[3 5] U50488H, a highly selective kappa opioid receptor agonist,[16] did not significantly alter gastric emptying or gastrointestinal transit.

When the fitted curves for the effect of each drug on gastric emptying and gastrointestinal transit are plotted in terms of percentage of control values (fig. 2), it is apparent that morphine nearly maximally inhibited both gastric emptying and gastrointestinal transit, whereas nalbuphine did not produce maximum inhibitory effects.

For each opioid the inhibitory effect on gastric emptying was similar to that on gastrointestinal transit. These results are in contrast to the effects of $alpha_2$ adrenoceptor agonists, which strongly inhibited transit in the small intestine, but only weakly inhibited gastric emptying.[15] Altogether, it is likely that the opioid receptor is involved in controlling both gastric emptying and intestinal transit, whereas the $alpha_2$ adrenoceptor is involved mainly in controlling intestinal transit.

OPIOID RECEPTOR TYPES FOR THE INHIBITORY EFFECT OF NALBUPHINE AND PENTAZOCINE

A partial agonist will show the following three features[1]: (1) the slope of the dose–response curve of a partial agonist is less steep than that of a full agonist; (2) there is a ceiling to its effect; and (3) a partial agonist will partially antagonize the effects of large doses of a full agonist.

The slope of the dose–response curve for nalbuphine was significantly less than that of morphine (table 2); there was a ceiling to its effect (fig. 2); and nalbuphine antagonized the inhibitory effect of morphine (table 3). These results are consistent with the characteristics of a partial agonist — in this case, a partial mu agonist.[1]

In contrast, for pentazocine, the slope of the dose–response curve did not differ significantly from that for morphine; there was no clear ceiling to its effect at the doses used; pentazocine did not significantly affect the inhibitory action of morphine. Therefore, it is likely that pentazocine delayed gastric emptying and gastrointestinal transit, not as a partial mu agonist, but possibly as a full mu opioid receptor agonist or a non-mu, non-kappa receptor agonist. The effect could be through the sigma receptor, as pentazocine has agonist activity at this receptor.[18 19]

Previous studies have shown that in some situations, nalbuphine acts as a partial mu agonist, whereas pentazocine cannot.[2 20–31] For example, nalbuphine antagonizes the antinociceptive effect of mu opioid receptor agonists.[2] It also antagonizes the inhibitory effect of mu opioid receptor agonists on respiration,[20 21] and decreases the incidence of nausea, vomiting and pruritus after injection of a mu receptor agonist.[22] In contrast, pentazocine does not generally antagonize the antinociceptive effect of morphine.[24–26] Although a few studies[19 25 27] showed that pentazocine antagonized the antinociceptive effect of morphine, this effect was considered to be mediated by the sigma receptor and the effect was not stereospecific.[19 27] In the isolated guinea-pig ileum, nalbuphine inhibited field-stimulation-induced contraction of the ileum through the mu opioid receptor, whereas pentazocine did so mainly through the kappa receptor.[30–31]

CLINICAL IMPLICATIONS

In humans, both nalbuphine and pentazocine significantly inhibited gastric emptying of liquids.[32–35] This is consistent with the results obtained in the present study in rats. However, it is not known whether there is a ceiling to the inhibitory effect of these drugs in humans, and whether they interact with morphine (or other strong mu receptor agonists) in a similar manner to that in rats.

The current and previous studies suggest that nalbuphine reduces the inhibitory effect of morphine on gastric emptying and intestinal transit, but it also reduces the antinociceptive effects. In contrast, pentazocine does not affect the antinociceptive effect of morphine or alter the inhibitory effect of morphine on gastric emptying and intestinal transit. Therefore, concurrent injection of nalbuphine and morphine or pentazocine and morphine, in theory, will not provide a potent analgesia with a relatively weak inhibitory effect on gastric emptying and intestinal transit. However, this theory needs to be tested in humans, because the pharmacological effects may differ between species.

In conclusion, we have found that, in the rat, a mu agonist (morphine), but not a kappa agonist (U50488H), delayed gastric emptying and gastrointestinal transit. Nalbuphine and pentazocine delayed these, possibly by different mechanisms; nalbuphine, but not pentazocine, acted as a partial mu opioid receptor agonist.

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REVIEW ARTICLE

The anaesthetist's role in acute sickle cell crisis

V. VIJAY, J. D. CAVENAGH, P. YATE

Over the past 30 years, there has been a significant increase in the life expectancy of patients suffering from sickle cell disease (SCD). In the early 1970s the median life expectancy was only 14.3 yr, whereas in the 1990s this has risen to 42 yr for men and 48 yr for women.[22 51] Nevertheless, there is a definite need to improve further the management of the acute complications of SCD, as these continue to cause significant morbidity and mortality. Furthermore, many patients are dissatisfied with their management during hospital admission.[20] We believe that the acute clinical problems of SCD, including pain, acute chest syndrome, thrombo-embolic disease and overwhelming infection, need expert management by a multidisciplinary team. Pain is by far the most common indication for hospital admission in these patients.[13 15 3] The primary requirement of the patient is therefore adequate pain relief. As a result of recent developments in the administration of analgesia, acute pain teams and, in particular, anaesthetists have become involved in the management of these patients with complex medical problems. In addition, the anaesthetist may be involved in the treatment of patients with sickle cell crisis perioperatively and in the intensive care unit.

Pathophysiology of sickle cell disease

Sickle cell disease (SCD) is a complex clinical entity characterized by an inherited, chronic haemolytic anaemia that is punctuated by a variable number of acute, painful vaso-occlusive episodes. The fundamental defect is the presence of a mutant haemoglobin (HbS) within the red cells of affected individuals; the defect is the consequence of a single-point mutation within the β-globin gene. This mutation results in a valine substitution for glutamic acid at position six of the β-globin molecule. The result is that, when the haemoglobin tetramer undergoes conformational change following deoxygenation, the hydrophobic valine residue is translocated to an external position on the globin molecule. In that position it interacts with other hydrophobic elements within neighbouring globin chains to form insoluble globin polymers. Polymerization of HbS after deoxygenation is the fundamental molecular event that underlies the protean clinical manifestations of SCD.

VASO-OCCLUSION

Vaso-occlusion is the single most important pathophysiological process that results in most of the acute complications of SCD.[69] Haemoglobin polymerization is the initial step in this process and significantly increases whole-blood viscosity. However, polymerized HbS rapidly reverts to normal once the haemoglobin molecule is re-oxygenated and the formation of irreversibly sickled cells (ISCs) is required for vaso-occlusion to occur. ISCs are formed as a consequence of irreversible oxidative damage to the cell membrane after repeated cycles of red cell sickling and unsickling. The oxidative damage occurs because HbS, in addition to having a propensity for polymerization, is an unstable haemoglobin and when exposed to oxidant stress elaborates a range of oxygen radicals. These highly reactive molecular species damage a wide variety of cytoplasmic, cytoskeletal and membrane proteins. The resultant ISCs have poor deformability and are prone to cellular dehydration; they are therefore removed prematurely from the circulation by the reticuloendothelial system. The altered membrane of sickled cells results in abnormal erythrocyte adhesion to endothelial cells and it is this process that initiates vascular occlusion.[36] The extent of sickle cell adhesion to endothelium *in vitro* is directly correlated with the clinical severity of vaso-occlusive phenomena in individual patients.[34] Once microvascular occlusion has occurred, the resultant hypoxia causes further sickling and the start of a vicious cycle that results in tissue infarction, the release of inflammatory cytokines and pain. The pathophysiology of the microvascular occlusion that occurs in SCD is discussed in more detail later.

GENOTYPES AND PHENOYPES IN SCD

SCD most commonly occurs in individuals who have the SS genotype, although patients heterozygous for HbS and β-thalassaemia (HbS/βThal) or HbS and haemoglobin C (HbSC) display a similar clinical phenotype. Sickle cell disease is increasingly prevalent in the UK, particularly in urban areas, and there are around 2000 patients in London alone. It is interesting that such a harmful mutation has not been eradicated from the gene pool by negative

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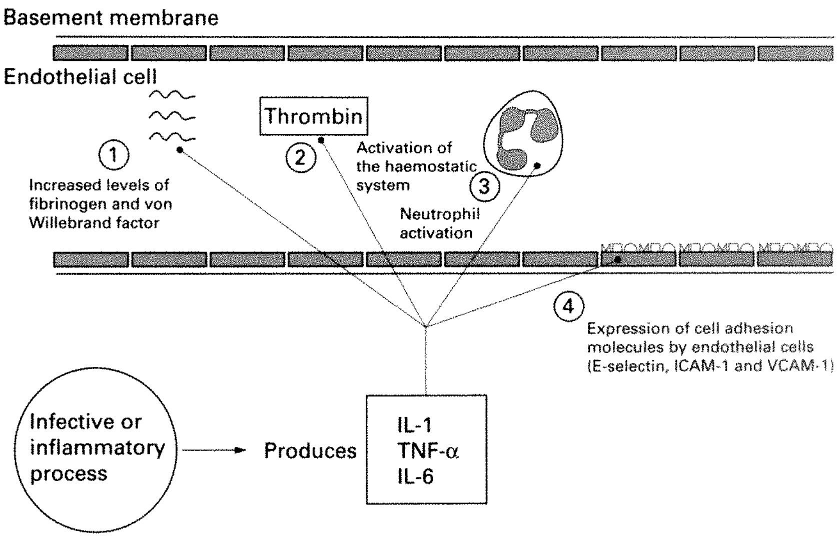
Basement membrane
Endothelial cell
Thrombin
①
Increased levels of fibrinogen and von Willebrand factor
②
Activation of the haemostatic system
③
Neutrophil activation
④
Expression of cell adhesion molecules by endothelial cells (E-selectin, ICAM-1 and VCAM-1)
Infective or inflammatory process
Produces
IL-1
TNF-α
IL-6

Figure 1 The microvascular occlusive process of sickle cell disease: stage 1. IL-1, interleukin 1; TNF-α, tumour necrosis factor-α; IL-6, interleukin-6; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1

selection pressure; the explanation appears to be that heterozygotes have a survival advantage over normals when infected by the malarial parasite *Plasmodium falciparum*. However, individuals with SCD itself are exquisitely vulnerable to overwhelming malarial infection.

The clinical phenotype of SCD is characterized by repeated vaso-occlusive events that can result in acute pain crisis, acute chest syndrome, priapism, stroke, skin ulceration and, in children, splenic sequestration. Autoinfarction of the spleen results in functional hyposplenism that is usually manifest by the age of 7 yr.[46] This, together with a variety of other defects in opsonization, phagocytic function and cell-mediated immunity, results in a greatly increased risk of systemic bacterial infection and infections at unusual sites, such as osteomyelitis and splenic abscesses.[62 18] Patients also suffer from a chronic haemolytic anaemia that results in poor growth, reduced fertility and gallstones. Erythropoiesis, while attempting to compensate for the rapid haemolysis, operates at near maximal levels; this renders the patient highly vulnerable to any further insult, such as folate deficiency, or Parvovirus infection, which causes pure red cell aplasia. In communities with inadequate parental education and poor availability of medical care, the major causes of early death in patients with SCD are overwhelming bacterial infection, splenic sequestration and, in tropical areas, malaria.

Clinical features

The two major acute complications of SCD that are likely to involve the anaesthetist are the acute pain crisis and the acute chest syndrome.

The acute pain crisis

Acute pain in SCD is thought to be caused by vascular occlusion and, in the case of bone pain, the consequent release of inflammatory mediators that results in raised intramedullary pressure and stimulation of nociceptors. Pain is the commonest manifestation of SCD after the age of 2 yr and painful episodes are most frequent from 20–40 yr of age. Large studies of the epidemiology and clinical presentations of pain crisis have highlighted several important points. The average rate of painful episodes is 0.8 per patient-year in sickle cell anaemia; however, 1% of these patients have more than six episodes per year, whereas some experience none.[50] Medical staff working in the acute health-care sector are likely to see only a few severely affected patients and may well develop misconceptions about the natural history of SCD. The extreme variability in severity of the clinical phenotype is largely unexplained. However, several important risk factors for recurrent painful episodes have been identified. SS or S/β^0Thal patients (β^0 indicates absence of β globin chain synthesis from the affected gene) tend to have more pain than those with the genotype S/β^+Thal (β^+ indicates reduced β globin chain synthesis from the affected gene) or SC, although many individuals with 'milder' genotypes experience more pain episodes than individuals with 'severe' genotypes. Patients with raised levels of haemoglobin F ($\alpha_2\gamma_2$), which inhibits the polymerization of HbS, have fewer painful episodes. Paradoxically, patients with lower haemoglobin levels have less pain. This is likely to be the result of lower whole blood viscosity associated with a lower haematocrit. This observation also explains why patients with coexistent α-thalassaemia trait, which results in a higher haematocrit, do not have a more benign clinical phenotype. Patients with more than three pain episodes per year are at a significantly increased risk of early death.[50] Among patients with repeated painful episodes, a few develop a chronic pain syndrome that results in restricted activity, fear of further pain and a high risk of depression.[8]

The ability to predict which individuals affected by sickle cell disease will go on to manifest a severe clinical phenotype would be of great clinical benefit. If such individuals could be identified in early life, they could be offered bone marrow transplantation in childhood, when this procedure is best tolerated.

Numerous precipitating factors have been identified for acute pain crises. Pain is more likely to start at night, perhaps because of nocturnal desaturation or relative dehydration. Other potential precipitants

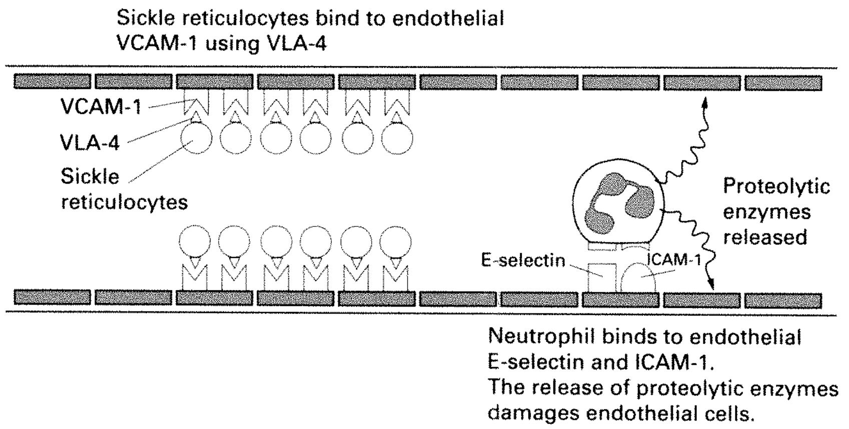
Sickle reticulocytes bind to endothelial VCAM-1 using VLA-4
VCAM-1
VLA-4
Sickle reticulocytes
Proteolytic enzymes released
E-selectin
ICAM-1
Neutrophil binds to endothelial E-selectin and ICAM-1.
The release of proteolytic enzymes damages endothelial cells.

Figure 2 The microvascular occlusive process of sickle cell disease: stage 2. VLA-4, very late activation antigen-4.

are exposure to cold, dehydration, alcohol intake, stress, menstruation and intercurrent infections.[63] However, 57% of episodes have no identifiable precipitant. The lumbar spine, femur, knee, sternum and abdomen are the most commonly affected sites. It is uncommon for pain to affect only one area and usually two or three sites are involved. An intriguing observation is the high frequency of symmetrical, bilateral bony pain. This observation has prompted the hypothesis that marrow ischaemia might result from a centrally mediated reflex that shunts blood flow away from the medullary cavity.[61]

The acute pain crisis is accompanied by fever in approximately 50% of cases but only in a few is an infective aetiology confirmed. The occurrence of fever, leucocytosis and an acute-phase response without evidence of microbiological infection has led to the consensus view that the acute pain crises itself initiates an acute inflammatory syndrome. Increasing knowledge about the adhesive mechanisms operating between circulating blood cells and vascular endothelium[16] has allowed the development of a unifying hypothesis that models the acute vaso-occlusive crisis.

Either a concurrent infective episode or an initial minor sickling event results in the elaboration by monocytes and macrophages of the inflammatory cytokines interleukin-1 (IL-1), tumour necrosis factor (TNF) and IL-6. These cytokines cause the upregulation of a variety of cell adhesion molecules (CAMs) on endothelial cells such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin.[10 33] The presence of these and other cytokines also leads to neutrophil activation, increased levels of pro-adhesive plasma proteins, such as fibrinogen and von Willebrand factor, and in the activation of the haemostatic system (fig. 1).

Alternatively, viral nucleic acid itself can induce CAM expression by endothelial cells.[65] Whatever the exact mechanism of upregulation, these endothelial CAMs can now mediate the adhesion of circulating cells. Normal mature red cells lack the necessary counter-receptors that bind to these CAMs but young reticulocytes, which are present in increased numbers in sickle cell disease, express CD36 and the integrin molecule VLA-4 and therefore bind to endothelium via VCAM-1 (fig. 2).[26 67]

It has been clearly established that sickle reticulocytes bind to vascular endothelium using this VLA-4/VCAM-1 adhesive pathway.[26] These cells are therefore retained in the relatively hypoxic environment of the postcapillary venule. Red cell sickling occurs then results in microvascular occlusion and distal ischaemia. Thus the vicious cycle of red cell sickling and vascular occlusion as outlined above is started and reinforced.

Furthermore, endothelial CAMs induced by inflammatory cytokines also bind platelets and neutrophils (via P-selectin, E-selectin and ICAM-1). Microvascular occlusion and resultant hypoxia, in addition to the release of proteolytic enzymes by the neutrophil, result in further endothelial damage (fig. 2). In turn, this is likely to activate the coagulation system, with consequent deposition of fibrin further obstructing blood flow (fig. 3).

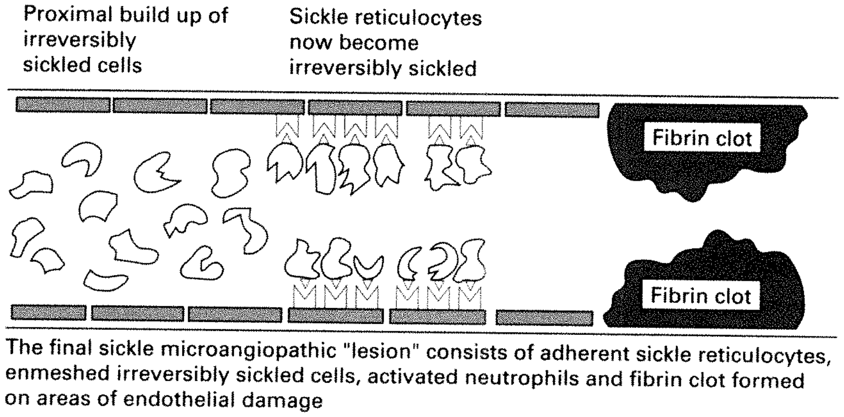
Proximal build up of irreversibly sickled cells
Sickle reticulocytes now become irreversibly sickled
Fibrin clot
Fibrin clot
The final sickle microangiopathic "lesion" consists of adherent sickle reticulocytes, enmeshed irreversibly sickled cells, activated neutrophils and fibrin clot formed on areas of endothelial damage

Figure 3 The microvascular occlusive process of sickle cell disease: stage 3.

Evidence for activation of the coagulation system in SCD exists. There are increased levels of prothrombin fragments 1 and 2 and of fibrinopeptide A in steady SCD.[49] Early attempts to reverse this prethrombotic state with oral anticoagulation achieved a reduction of acute painful crises but at the cost of an unacceptably high risk of haemorrhage.[60] More recently, it has been realized that low-dose coumarin therapy can normalize this prethrombotic state, although it is uncertain whether this approach can be of benefit in preventing the acute crises of SCD.[72]

The acute pain crisis of SCD results from the cumulative effects of HbS polymerization, red cell sickling, sickle cell adhesion to vascular endothelium and fibrin deposition; all of these act together to cause microvascular occlusion.

PREVENTION OF PAIN CRISIS IN SCD

Various methods have been tried over the past few years to prevent or reduce recurrent sickle cell crises. Hydroxyurea and other agents have been used in an attempt to increase the production of HbF, inhibiting HbS polymerization.[30] [56] Induced hyponatraemia has been used to reduce the erythrocyte HbS concentration, but has proved impractical.[57] Advice on lifestyle can be useful, such as avoiding excess alcohol consumption; the consequent dehydration can precipitate a pain crisis.

Pre-operative transfusion

Surgery is a time of special risk for patients with SCD and in an attempt to reduce complications, including painful crises, it has become standard practice to consider the use of preoperative blood transfusions. In a large retrospective study of surgery in SCD[40] there was in general no correlation between the rate of postoperative complications and the HbA level (which is directly proportional to the extent of red cell transfusion). Furthermore, the rate of complications after minor procedures was low in patients who had received no transfusions. A recent prospective study evaluated the relative efficacies of an aggressive perioperative transfusion policy (aimed at reducing the HbS level to below 30%) and a conservative policy (aimed at raising the Hb level to above10 g dl^{-1}) in patients with SCD undergoing elective surgery. The frequency of serious complications was similar in both groups but there were twice the number of transfusion-related complications, especially the development of red cell alloantibodies, in the aggressively transfused group.[70]

Therefore, in patients about to undergo elective procedures of intermediate or high risk, a relatively conservative transfusion programme aimed at raising the Hb to above 10 g dl^{-1} can be recommended. For minor procedures, there appears to be little benefit in perioperative transfusion. In contrast, patients who require emergency surgery are often those at greatest risk of postoperative SCD-related complications. The optimal transfusion support for individual patients should be discussed by the surgeon, anaesthetist and haematologist.

MANAGEMENT OF CRISIS

The mainstays of management of pain crisis are analgesia and fluid replacement. Oral or intravenous fluids are required to prevent dehydration, which results in a raised haematocrit and increased sickling. Although fever may be a simple consequence of sickling, the presence of fever should prompt a search for an infective focus and cultures of blood, urine and sputum should be taken as indicated.

As there is a high risk of bacterial infection in patients with SCD, most clinicians would recommend the use of broad-spectrum antibiotics in the presence of fever. Functional hyposplenism makes these patients susceptible to streptococcal infection; and the chosen agent (e.g. amoxycillin) must have good activity against *Streptococcus pneumoniae.* Blood transfusion has a place in acute crisis only in the presence of the acute chest syndrome (see below) or stroke, or when a pain crisis is refractory to standard therapy or relapses quickly. In view of the considerable inflammatory element in the acute pain crisis, a trial of high-dose methylprednisolone — two doses of 15 mg kg^{-1}, 24 h apart, has been undertaken. The requirement for opioid analgesia was considerably reduced in the steroid-treated group, and the mean duration of analgesic treatment was reduced from 71.3 to 41.3 h. However, a high rate of rebound attacks was observed and this, in addition to fear of the long-term complications of steroid therapy, has restricted the use of this treatment strategy.[32]

Most painful episodes are managed at home by the patients themselves, with oral analgesia and fluids. Episodes of crisis may last from a few minutes to weeks and the severity and location of the pain may vary from time to time or involve the whole body.[38] [69] Younger children often suffer from limb pain. In contrast, in adolescents, abdominal pain may become the prominent symptom. The few crises that result in hospital attendance often require more intensive analgesia. Accident and emergency staff with limited experience of SCD may underestimate the severity of pain, because no objective criteria accurately quantify it. The result may be unnecessary suffering, inadequate pain control or misinterpretation of the patient's demands.[71] [2] The pain of sickle cell crisis is probably one of the most severe forms of pain. The intensity and description of pain during crisis have been studied and the average pain severity score was 9.5 ± 0.63 on a 10 cm visual analogue scale.[7]

The use of large doses of opioids for pain relief has raised concerns about the risk of drug dependence,[45] but this has been disputed. In a 1986 survey of 610 patients with sickle cell disease from five institutes in a North London borough, none was known to be addicted, in spite of a local policy of using strong opioids to relieve the pain of crisis.[14] Similarly the use of parenteral opioids is widespread in major sickle cell disease treatment centres in the USA.[47] Clinicians working in tropical countries and those in Britain and the USA seem to diverge markedly in their views on the need for opioids.[39]

It is important to distinguish between tolerance to opioids and addiction. Most patients with sickle cell crisis requiring prolonged treatment with opioids will develop tolerance, and on discontinuing opioids exhibit some signs of withdrawal. The latter can be minimised by a gradual withdrawal of opioids. Clinicians who are relatively inexperienced in the management of sickle cell crisis may interpret evidence of tolerance or withdrawal as being indicative of a state of addiction, and understandably this may cause considerable patient distress. But it is vital to realize that many episodes of pain are undertreated. This undertreatment will lead to an increased fear of future episodes and may well contribute to the development of a chronic pain syndrome. The patient's ability to cope with the present painful situation depends on his or her previous experience of pain relief and the treatment received in hospital, as well as family relationships and social circumstances. The unpredictability and severity of these crises may result in the phenomenon of "learned helplessness" observed in animals. When these animals are exposed to repetitive, unpredictable shocks, their ability to escape shocks in future become severely impaired.[41]

AN INVISIBLE CHRONIC ILLNESS

In common with other chronic pain syndromes, there appears to be considerable variation in the coping abilities of patients with sickle cell disease.[29] Among children, frequent hospital admissions with painful crises, separation from the family and feelings of 'being different' seem to be significant problems. Cohesive family relationships as well as sympathetic staff at school and hospital all seem to improve coping mechanisms. For adolescents, anxieties about delayed physical maturity combined with interruption of normal teenage activities can result in feelings of isolation. These factors, together with fears of a potential early death or of academic failure, are among the main reasons for the psychological instability in this group of patients.[1] The lack of visible stigmata associated with SCD may prompt mistrust and suspicion on the part of care providers and family members, resulting in a loss of self-esteem, depression and violence.[35] Active coping suggestions, reassurance and positive behaviour by adults providing care for these patients have been shown to enhance their coping strategies.[8, 37] Males are more likely to have psychosocial dysfunction, particularly at adolescence.[43]

MODES OF ANALGESIA IN SCD

The choice of analgesic drugs includes nonsteroidal anti-inflammatory agents (NSAIDs), which are particularly helpful for bone pain, and a variety of opioid analgesics (see below). In certain situations, the use of local anaesthetics and extradural anaesthesia can be considered. Analgesics ranging in potency from paracetamol to strong opioids can be administered orally during a crisis without the need for an intravenous cannula. However, the onset of such analgesia is then not immediate and the efficacy depends upon the rate of absorption and bioavailability. Absorption may also be influenced by the presence of nausea and vomiting.[25]

Transdermal administration

Transdermal fentanyl patches are effective in postoperative pain. These patches are easy to adminster and contain multiday dosage, but stable plasma levels may not be reached for 12 h after application. The main disadvantages of the patches are that analgesia is slow in onset and difficult to titrate against response, and that a residual depot is left after removal of the patch.[52, 58] We have used fentanyl patches successfully in a few patients in the later stages of admission for acute sickle cell crisis and have discharged the patients home with them.

Intramuscular administration

The intramuscular route offers simplicity with a relatively rapid onset of analgesia after injection. This mode of delivery may be useful for initial analgesia when the patient arrives in hospital before the establishment of venous access, which can itself be problematic. However, repeated intramuscular injections are painful and may result in myofibrosis, myositis and the formation of abscesses. In addition, pain relief may be inadequate because the rate of absorption is unpredictable. The peak concentration of pethidine may vary two-fold and time to reach peak concentration may vary three-fold with repeated intramuscular injections in the same patient.[4, 5] Subcutaneous infusions are simple and effective but the unpredictable rate of absorption from the site results in a variable quality of analgesia.

Intravenous administration

Venous access is almost always required for hydration and for the administration of antibiotics. Early involvement of anaesthetists from the acute pain team may lessen the problems encountered when attempting to secure i.v. access. Analgesia by continuous i.v. infusion is safe and effective.[19, 55] Doses required may be higher than those used for the routine management of postoperative pain. A protocol described for children recommended a loading dose of pethidine 1.0 mg kg^{-1} followed by an infusion of 0.5 mg kg^{-1} h^{-1} although some patients required doses up to 1.5 g k^{-1} h^{-1}. When this protocol was used in a series of 98 patients, none exhibited signs of dependency or withdrawal when the infusion was discontinued. Severity of pain may fluctuate with time and continuous infusions may provide inadequate pain relief or a risk of overdosage. This is illustrated in a case report of a boy aged 15 yr, in whom the uncontrolled administration of morphine, without proper monitoring and in the presence of decreasing pain, led to respiratory depression, acidosis, increased sickling, and ultimately cardiopulmonary arrest.[28]

Patient-controlled analgesia

Patient-controlled analgesia (PCA) is widely used for pain relief after surgery and may well be superior to more traditional methods of pain relief; however, its place in the management of sickle cell crisis has yet to be fully established. Nevertheless, in sickle cell crisis, PCA has been reported to improve the adequacy of pain relief when the latter is suboptimal because of insufficient dosage or delay in administration. It can also match the individual variability of analgesic demand and enables the patient to administer his or her own analgesia.[31] A prospective controlled trial of morphine PCA in patients with SCD, using bolus mode only, showed that PCA was as effective as an aggressive fixed schedule of intermittent, nurse-administered i.v. injections of morphine. Among the advantages of PCA identified by nurses in this study were convenience and increased involvement of patients with their own care. The disadvantages included a long set-up time. Of these patients, 80% described the PCA analgesic regimen as good to excellent.[64]

One difficulty with fixed dosing when compared with PCA is the enormous variability of opioid pharmacokinetics. A recent study of morphine use in children with sickle cell disease found morphine clearances ranging from 6.2 to 59 ml min^{-1} kg^{-1}.[21] In another series of 46 children and adolescents receiving morphine, nalbuphine or hydromorphone PCA, 30% had problems. Eleven patients disliked the technique, one patient required naloxone and one tampered with the machine.[64] To reduce the need for extra venepuncture, the main i.v. infusion line can be used for the PCA if an anti-reflux valve is used.

All patients should be monitored with a pain chart. In our unit, pain scores achieved with PCA were less satisfactory in patients with acute sickle cell crisis compared with those recovering from surgery. With a five-point pain score, 95% of observations in postoperative patients were below 3, whereas only 26% of those in patients with acute sickle cell crisis had a pain score of less than 3. Many patients with sickle cell crisis felt comfortable enough to request discontinuation of their PCA, while still recording their pain as severe. Most patients with sickle cell crisis require both a background infusion and demand dosing during the initial acute episode. The background infusion is tailed down with improving pain scores before discontinuing the demand dosing, but the presence of a background infusion may reduce the safety of this technique. Tolerance to the effect of opioids can develop rapidly and it is not uncommon for patients to require very large doses at some period during their admission. With large doses, problems such as pruritus, dysphoria, hallucinations and respiratory depression can be troublesome, with many patients requiring antipruritic and antiemetic agents.

Slow-release oral opioids

An alternative strategy is to manage the pain of sickle cell disease in the same way as one would manage pain associated with cancer. Thus, rather than offering strong analgesia only during admissions for severe crisis, one may prescribe regular slow-release morphine to outpatients with the addition of a small amount of standard morphine for breakthrough pain. The authors who tried this approach claimed a dramatic reduction in hospital admissions.[12] However, a subsequent report suggested that this observation might be the result of patients attending alternative institutions for their care.[6] It is well known that patients with sickle cell disease will transfer to another institution if a new or unpopular analgesic regimen is introduced, particularly the substitution of other opioids for pethidine.

Extradural analgesia

Extradural analgesia has been used in the management of acute sickle cell crisis. Recent evidence suggests that it might be superior in sickle cell patients with localized pain who are unresponsive to high-dose systemic opioids, nonsteroidal drugs or adjunctive measures.[74] Continuous local anaesthetic infusions and a combination of local anaesthetic with fentanyl seem to be effective with minimal opioid-related side-effects. Inadvertent dural puncture and hypotension following a higher block may be a concern.

PHARMACOLOGICAL AGENTS FOR SICKLE CELL CRISIS

Opioid analgesics

Opioid analgesics agents bind to specific opioid receptors — μ, χ and σ — and block slow transmission of pain. Efficacy of analgesia and unwanted side-effects are determined by the relative affinity of these agents for the individual receptors. Pethidine seems to be the opioid chosen most often by sickle cell patients. Familiarity, degree of predictability and belief that pethidine produces a rapid onset of analgesia with less "hangover", make pethidine the first choice for many patients with sickle cell crisis.[42] In a comparison of pethidine with morphine in children, subjective side-effects including lethargy, abdominal distension, constipation, pruritus and wheezing were less common with pethidine, although dizziness was more common.[19] The main disadvantage of pethidine is attributable to its metabolite, norpethidine. Norpethidine significantly stimulates the central nervous system and daily doses of pethidine in excess of 25 mg kg^{-1} are associated with blood levels of norpethidine high enough to precipitate convulsions.[54] In a survey of 21 major centres treating sickle cell disease in the USA, nine reported problems with pethidine-associated convulsions.[47] The recognized risk factors for norpethidine-related convulsions are renal failure, high pethidine dosage and co-administration of hepatic enzyme inducers.

Pethidine has also been shown in dogs to impair cardiac performance by reducing myocardial contractility when doses exceed 2 mg kg^{-1}.[24] For these reasons it is widely accepted by physicians looking after patients with acute sickle cell crisis that pethidine should be avoided whenever possible. However, this may prove unacceptable to a few patients with sickle cell crisis who may insist on the drug. It is advisable not to use pethidine as a first-choice analgesic for new patients or those unfamiliar with pethidine, but reserve it for those patients who experience unacceptable side-effects, such as pruritus, with other strong analgesics.

Morphine is often used as the opioid of choice for initial treatment, when a strong analgesic is required. Excessive sedation is a recognized problem, in addition to other opioid-related side-effects such as itching, respiratory depression, nausea and vomiting. In

Table 1 Guidelines for pain relief in sickle cell crisis (Royal London Hospital)

Acceptable pain relief to be achieved safely with minimal delay when patient arrives at hospital — immediate involvement of the Acute Pain Team

Preferred mode of analgesia is patient-controlled analgesia (PCA) using i.v. fentanyl

Intermittent analgesia by i.m. injection may be the patient's preferred option. Suitable regimens for an adult would be:
  Morphine 7.5–15 mg, every 2–4 h
  Diamorphine 2.5–5.0 mg, every 2–4 h
  Cyclizine 50 mg, every 6–8 h for anti-emesis
Dosage may be adjusted according to:
  1. Previous drug regimen
  2. Severity of pain
  3. Size of the patient

NSAIDs should be prescribed, unless contraindicated in a particular patient

Monitor pain management. Start pain chart when giving initial analgesia

the presence of renal impairment, morphine-6-glucuronide, which is an active metabolite of morphine, may accumulate and cause respiratory depression.[44] Diamorphine can be used in preference to morphine, having a more rapid onset of action and greater potency. Fentanyl, a synthetic opioid derived from pethidine, is also a potent analgesic, and its high lipid solubility results in a rapid onset of action. Fentanyl is a useful drug in patients with SCD bcause of its cardiovascular stability, lack of histamine release even with large doses, and absence of active metabolites. It is relatively nonsedative and can be used in patients with renal failure and mild hepatic dysfunction. Fentanyl administered by PCA is the analgesic mode of choice in our unit.

Nonopioid agents

Aspirin and other NSAIDs can be of use in bony crisis, to alleviate mild to moderate pain and as an adjunct to opioids in a severe crisis.[48] However, one study was unable to identify any opioid-sparing activity using ketorolac in the emergency room.[73] The antiplatelet activity of these compounds may also be beneficial in patients who are susceptible to venous thrombosis. However, in view of the renal impairment associated with NSAIDS, care must be taken with their use.

Adjuvant drugs

Patients with SCD may develop features of a chronic pain syndrome. Some psychotropic drugs, particularly tricyclic antidepressants such as amitriptyline, possess analgesic properties that may be useful in the management of SCD.[53] These agents inhibit the reuptake of noradrenaline and 5-hydroxytryptamine, which are released by descending systems of supraspinal origin, thus modulating the nociceptive input into the spinal cord. Benzodiazepines are of value in relieving muscle spasm, anxiety and insomnia.

NON PHARMACOLOGICAL METHODS OF PAIN CONTROL

Non pharmacological methods of pain control are used to alleviate stress, to increase the individual's ability to cope with acute and chronic pain, and to improve the patient's sense of well-being. Although these methods have not been extensively tested in sickle cell disease, some modalities such as diversion techniques, self-motivation, massage and mechanical stimulation are beneficial in some patients. The main value of stimulation techniques may be in the treatment of localized pain. Cognitive-behavioural methods modulate the affective response to pain by acting at the level of the cerebral cortex, limbic system and reticular formation.

Self-hypnosis, bio-feedback, relaxation and cognitive methods have been used successfully in reducing pain symptoms, hospital admissions and the use of opioids during painful episodes.[75] Recently, acupuncture has been found to be effective in treating a few patients with sickle cell crisis when conventional therapies have failed.[66]

The acute chest syndrome

The acute chest syndrome (ACS) is one of the most serious complications of SCD, with a mortality approaching 10%. Its pathogenesis is not clearly understood.[17] Bacterial pneumonia, pulmonary thromboembolism and infarcted marrow embolism can all cause acute respiratory compromise. Many cases have no recognizable infective or embolic causation. Progressive pulmonary fibrosis has been detected in children with multiple episodes of acute chest crisis.[11]

Typically, such cases present with an acute pain crisis, often affecting the lower chest wall. Patients quickly develop fever, cough, chest signs, radiological changes — usually affecting the bases of the lungs — and oxygen desaturation on air. The radiological changes may be delayed.[68] A substantial number of these patients have rib infarcts[27 59] and it is thought that the resulting splinting of the lower chest wall with basal hypoventilation results in rapidly progressive intrapulmonary vaso-occlusion, hypoxaemia, increasing pulmonary problems and ACS.

Evidence for this model is the reduced development of pulmonary complications with the use of prophylactic incentive spirometry.[9] There are concerns that narcotic analgesics, with their associated respiratory suppression, may contribute to the acute chest syndrome,[19] although adequate analgesia is probably essential to prevent atelectasis.[27]

The acute chest syndrome should be treated as a medical emergency and adequate oxygenation ensured by increased inspired oxygen concentrations; continuous positive airway pressure (CPAP) to maintain ventilation of the lung bases; and, if necessary, mechanical ventilation. The early use of exchange transfusion, with the aim of achieving an HbS% of more than 30% will abort further deterioration and usually reverses respiratory failure within 1–2 days. An alveolar–arterial oxygen gradient of more than 30 mm Hg on air is a predictor of both clinical severity and the need for exchange blood transfusion.[23] The rapidity of the response to exchange transfusion strongly supports the theory that reversible vaso-occlusion, rather than thromboembolism or infection, is the major pathophysiological process in ACS. However, an infective aetiology can never be excluded in an individual case and it is mandatory to treat patients with broad-spectrum antibiotics active against common respiratory bacteria and atypical pathogens.

Conclusion

Most patients with sickle cell disease are managed in the community by their general practitioner in consultation with haematologists and specialist nurses. However, as patients in crisis may arrive outside routine working hours, their first medical contact may be with a relatively inexperienced junior doctor. We recommend therefore that management guidelines are provided for the initial management of patients presenting with the acute complications of SCD (table 1).

Undoubtedly, on arrival at hospital, the primary requirement for patients with sickle cell crisis is adequate analgesia followed by admission to a dedicated unit. This can best be achieved by careful teamwork involving haematologists, ward nurses and members of the acute pain team.

Management of the acute pain crisis should be seen in the context of the overall long-term strategy for the care of patients with SCD, which should include patient education, prophylactic folic acid and penicillin V. Vaccination against the organisms most likely to cause problems in the hyposplenic individual (namely *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae* type b) is appropriate.

Various approaches have been tried, or are under investigation, in an attempt to reduce the frequency of acute painful crises. Regular exchange blood transfusion with appropriate iron chelation, antioxidant drugs, agents that prevent sickle cell dehydration and drugs that increase the haemoglobin F concentration are among such strategies. Combined input from pain specialists, anaesthetists, haematologists, sickle cell nurse specialists and psychologists, together with the formation of self-help groups, will undoubtedly improve the quality of the service provided for these patients.

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SHORT COMMUNICATIONS

Changes in arterial–mixed venous oxygen content difference (Ca_{O_2}–$C\bar{v}_{O_2}$) and the effect on shunt calculations in critically ill patients

M. NIRMALAN, T. WILLARD, A. KHAN, P. NIGHTINGALE

Summary

Many commonly used indices of pulmonary oxygen transfer assume that Ca_{O_2}–$C\bar{v}_{O_2}$ is constant. We studied changes in Ca_{O_2}–$C\bar{v}_{O_2}$ in critically ill patients to determine the effect on calculated shunt of assuming a fixed Ca_{O_2}–$C\bar{v}_{O_2}$. Two hundred pairs of arterial and mixed venous blood gas measurements were obtained retrospectively from 43 patients, each providing four or five pairs from a period of 48 h. Ca_{O_2}–$C\bar{v}_{O_2}$ ranged from 13 to 74 ml l^{-1}. The mean within-patient SD was 6.8 ml l^{-1} and the overall between-patient SD was 10.9 ml l^{-1}. Our results show that assuming a fixed Ca_{O_2}–$C\bar{v}_{O_2}$ leads to errors in quantifying pulmonary oxygen transfer. (*Br. J. Anaesth.* 1998; **80**: 829–831)

Keywords: intensive care; oxygen transfer pulmonary; oxygenation indices

Shunt fraction (Q_s/Q_t) is the most accurate index commonly available to quantify impairment of pulmonary oxygen transfer. The value of Q_s/Q_t is calculated using the equation:

$$Q_s/Q_t = (Cc'_{O_2}-Ca_{O_2})/(Cc'_{O_2}-C\bar{v}_{O_2})$$

(where Cc'_{O_2}, Ca_{O_2}, and $C\bar{v}_{O_2}$ are the oxygen content of end-capillary, arterial and mixed venous blood respectively). When mixed venous blood is not sampled, methods using a fixed Ca_{O_2}–$C\bar{v}_{O_2}$ are considered possible surrogates. "Virtual shunt" and "iso-shunt charts" are two such methods where Ca_{O_2}–$C\bar{v}_{O_2}$ is given a fixed value of 50 ml l^{-1}.[1] If Ca_{O_2}–$C\bar{v}_{O_2}$ should vary, this can cause changes in "virtual shunt" that, if large, could become clinically misleading. This is particularly relevant in patients in whom serial measurements of shunt are used to determine changes in oxygen transfer.

Mean Ca_{O_2}–$C\bar{v}_{O_2}$ is approximately 35 ml l^{-1} in critically ill patients,[2] but changes in Ca_{O_2}–$C\bar{v}_{O_2}$ are more important than absolute values when assuming Ca_{O_2}–$C\bar{v}_{O_2}$ to quantify oxygenation defects. These changes have not been studied previously and the present study was undertaken to determine variations in Ca_{O_2}–$C\bar{v}_{O_2}$ and to evaluate the effect of such changes on shunt calculations.

Methods and results

We collected 200 pairs of arterial and mixed venous blood gas measurements retrospectively from 43 patients who were treated in an ICU over a period of 10 months. All patients with four or more shunt measurements during any 48 h of their stay were included in the study and four or five readings were obtained from each patient. FI_{O_2} had been set according to clinical need (range 0.35–1.0). The position of the pulmonary artery catheter was confirmed radiologically in all patients. The ICU where the study was carried out takes part in a National Quality Assurance Programme, requiring regular automated calibration of the blood gas machine and co-oximeter (BGE and IL282-Instrumentation Laboratory, Italy). Externally referenced samples are analysed regularly to confirm the accuracy of the system as part of this programme. The measuring range for Pa_{O_2} was 0–106 kPa with a resolution of 0.1 kPa (coefficient of variation not greater than 1.3%). The system measures oxygen tension, oxygen saturation and haemoglobin concentration and calculates oxygen content and shunt fractions, as outlined in the operator's manual.

We found that Ca_{O_2}–$C\bar{v}_{O_2}$ ranged from 13 ml l^{-1} to 74 ml l^{-1} (mean 35.6 ml l^{-1}). The mean within-patient SD was 6.8 ml l^{-1} and the overall between-patient SD 10.9 ml l^{-1}.

The effect of assuming a fixed Ca_{O_2}–$C\bar{v}_{O_2}$ for shunt calculations in the presence of the above variability was then studied using an iso-shunt chart described by Benatar and colleagues.[3] There were 188 readings (from 40 patients) within the specified range for iso-shunt charts for comparison. Each measured shunt fraction was compared with the corresponding shunt values interpolated from the charts, using the method of Bland and Altman[4] and two-way analysis of variance for repeated measurements.

The correlation coefficient between measured shunt and estimated shunt was 0.62. The chart underestimated shunt fraction with a mean bias of 6.5% (confidence interval 1.1%) with wide limits of agreement (2 SD 16%) (fig. 1). The difference was statistically significant ($P < 0.001$ for F ratio).

In 23 patients there was no change in estimated shunt with changes in measured $Q_s/Q_t < 10\%$ and in 11 the changes in estimated and measured values were in the opposite direction at least once. In one patient, a change in $Q_s/Q_t > 10\%$ was not detected by the chart as it was masked by concurrent changes in Ca_{O_2}–$C\bar{v}_{O_2}$.

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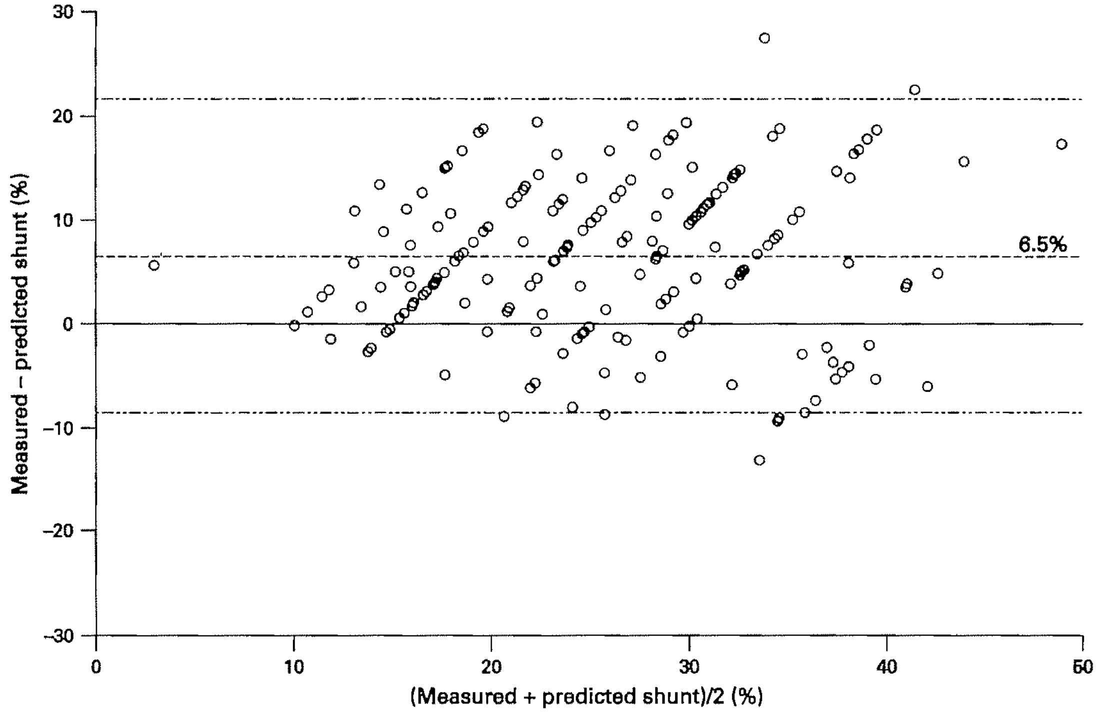

Figure 1 Agreement between measured shunt and that estimated from the iso-shunt chart.

Comment

We corroborate the findings of Harrison and colleagues that the mean Ca_{O_2}–$C\bar{v}_{O_2}$ in critically ill patients is approximately 35ml l^{-1}.[2] The assumption of a constant Ca_{O_2}–$C\bar{v}_{O_2}$ is common to many estimates of oxygen transfer, but changes in Ca_{O_2}–$C\bar{v}_{O_2}$ are frequent and can occur within relatively short periods. Lawler and colleagues found a 20% change in Ca_{O_2}–$C\bar{v}_{O_2}$ within approximately 2 h, in a patient who seemed clinically stable.[1] Changes in clinical condition and in therapy such as ventilation, fluid administration and vasoactive drugs may change oxygen delivery, consumption or both and thereby could alter Ca_{O_2}–$C\bar{v}_{O_2}$. We have quantified this variability and have shown that assuming a fixed Ca_{O_2}–$C\bar{v}_{O_2}$ will hamper interpretation of changes in oxygen transfer. Using sampled values of Pa_{O_2}, FI_{O_2}, arterial blood and mixed venous blood our model shows how a measured change in Ca_{O_2}–$C\bar{v}_{O_2}$ of more than 27 ml l^{-1} could mask an actual change in shunt of more than 10%. Assuming a Ca_{O_2}–$C\bar{v}_{O_2}$ of 35 ml l^{-1} will minimize the bias between measured and estimated shunt (bias 0.23; $P > 0.5$ for F ratio). Similar observations were made by Cane and colleagues[5] but the limits of agreement are unchanged, so the accuracy of such estimates remain poor. The modification of iso-shunt charts proposed by Petros and colleagues[6] was not used, as all patients received an $FI_{O_2} > 0.35$. Shunt calculations are inaccurate at high FI_{O_2} because of errors in measuring high Pa_{O_2}[1]; however, the Pa_{O_2} range in our patients (7.9 kPa–76 kPa) was well within the measuring range of the blood gas machine. Potential errors in measurement should therefore have minimal influence on our findings.

Interest in use of the Pa_{O_2}/FI_{O_2} ratio to assess defects of oxygen transfer was renewed by the work of Gowda and colleagues.[7] They showed that Pa_{O_2}/FI_{O_2} ratio, unlike measured shunt, was relatively independent of changes in FI_{O_2} in patients with adult respiratory distress syndrome (ARDS), in the presence of ventilation/perfusion abnormalities and severe hypoxaemia (shunt fraction >30% and $Pa_{O_2} <$ 13.3 kPa). However they assumed that Ca_{O_2}–$C\bar{v}_{O_2}$ was constant or altered minimally. Patients with severe ARDS often have multiple organ failure requiring treatment that could alter Ca_{O_2}–$C\bar{v}_{O_2}$. In a hypothetical patient with a 35% shunt receiving an FI_{O_2} of 0.7 and a mean Ca_{O_2}–$C\bar{v}_{O_2}$ of 35.6 ml l^{-1}, a variation of 13.6 ml l^{-1} (2 SD of the within-patient variation) would alter the Pa_{O_2}/FI_{O_2} ratio between 91 and 195. Such a variation could be misleading in the management of such patients. The correlation between measured shunt fraction and Pa_{O_2}/FI_{O_2} ratio in our patients on $FI_{O_2} > 0.5$ ($n = 32$) was similar to the correlation between measured shunt and that estimated by the isoshunt chart ($r = -0.56$).

The indices referred to above are used to quantify oxygen transfer. They do not necessarily reflect the severity of the underlying lung injury or the patient's illness, and by and large do not predict clinical outcome satisfactorily. The dynamic changes induced by altering oxygen administration are an integral part of the processes that influence oxygenation. Therefore in spite of being altered by FI_{O_2}, measured shunt fraction remains the best measure of oxygen transfer taking into consideration factors such as the underlying lung injury, effect of FI_{O_2} changes and the mode of respiratory support.

We conclude that the changes in Ca_{O_2}–$C\bar{v}_{O_2}$ seen in critically ill patients preclude the assumption of a fixed Ca_{O_2}–$C\bar{v}_{O_2}$ value in quantifying oxygen transfer. There is no substitute for measured shunt fraction, and it is important to re-evaluate published work where indices of oxygen transfer that assume a fixed Ca_{O_2}–$C\bar{v}_{O_2}$ have been used to evaluate outcome.

Acknowledgement

We thank Dr M Columb, FRCA, for critical advice.

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Myocardial ischaemia during tracheal extubation in patients after cardiac surgery: an observational study

N. J. BARHAM, O. W. BOOMERS, K. M. SHERRY, T. J. LOCKE

Summary

This study examines whether there is a temporal relationship between tracheal extubation and myocardial ischaemia in haemodynamically stable patients extubated within 6 h of cardiac surgery. Fifty-two patients were studied during three time periods: 1, from 2 h until 30 min before extubation (90 min); 2, from 30 min before until 30 min after extubation (60 min); 3, from 30 min until 2 h after extubation (90 min). Significant ST segment changes were defined as a reversible ST segment depression of 2 mm or greater or an elevation of 3 mm or greater from baseline, lasting for 1 min or more. Fourteen patients (26.9%) had ST segment changes. The ischaemic burden in periods 2 and 3 was increased compared with that in period 1; the mean (SD) was: period 1, 19.2 (18.8) min; period 2, 35.4 (24.9) min; period 3, 39.6 (24.5) min; however, the mean ST deviation (mm) did not change. ST segment changes were associated with an increased heart rate; they were not related to arterial pressure. We conclude that there is a temporal relationship between ST segment changes and tracheal extubation after cardiac surgery. (*Br. J. Anaesth.* 1998; **80**: 832–833)

Keywords: heart ischaemia; surgery cardiac; intubation tracheal extubation

After general surgery, patients at risk of myocardial ischaemia may have ST segment abnormalities during tracheal extubation.[1] Patients are also at risk of myocardial ischaemia after coronary artery surgery, particularly during the first 2 days after operation.[2] The aim of the present observational study is to determine if there is a temporal relationship between ST segment abnormalities and tracheal extubation within 6 h of coronary artery surgery.

Methods and results

After obtaining local Ethics Committee approval and written informed consent, we studied 52 patients undergoing elective coronary artery surgery as a sole procedure. Patients were excluded if they had factors that make ST segment changes difficult to interpret, such as left ventricular hypertrophy or left bundle branch block or if they were receiving digoxin or cardiac pacing. Patients taking cardiac medication continued to do so, including on the morning of surgery. All patients were premedicated with morphine 10 mg i.m. 1 h before operation. Anaesthesia was induced with fentanyl 10–15 μg kg^{-1} supplemented with isoflurane or propofol. Tracheal intubation was facilitated with pancuronium 0.1-0.15 mg kg^{-1} and the lungs ventilated with an air–oxygen mixture to maintain normoxia and normocarbia. Cardiopulmonary bypass included an 1800 ml Plasmalyte prime and a membrane oxygenator. Myocardial preservation during the aortic cross clamp was provided by anterograde cold crystalloid or blood cardioplegia, and moderate hypothermia (30–32°C) was used. After cardiopulmonary bypass all patients received an infusion of glyceryl trinitrate 0.3–2.0 μg kg^{-1} min^{-1} and some received low-dose inotropic support (dobutamine or dopamine at less than 3 μg kg^{-1} min^{-1}). After transfer to the intensive care unit, all patients received elective positive pressure ventilation of the lungs with an $F_{I_{O_2}}$ of 0.6. During positive pressure ventilation, all patients received morphine 2 mg i.v. for analgesia and sedation; some patients received additional sedation with a propofol infusion, 1–2 mg kg^{-1} h^{-1}. The ST segments of electrocardiograph (ECG) leads V2 and V5 were continuously monitored in each patient, from arrival in the intensive care unit until at least 2 h after tracheal extubation, using the Compass ST segment analyser (Cardiac Care Units, Inc., California, USA). This analyser is a microprocessor-based, solid-state, portable four-lead monitor that stores digitally the automated continuous ECG analysis. After each monitoring session it generates a time-correlated printout reporting ST segment changes. Patients were considered ready for tracheal extubation if they were normothermic, awake, haemodynamically stable, on no or minimal inotropic support and had good gas exchange. Before extubation they were assessed, while intubated and breathing spontaneously on a 'T' piece with an $F_{I_{O_2}}$ of 0.6 for less than 30 min. The time of extubation was used as the reference time. Three time periods were analysed for ST segment changes. These were: 1, from 2 h until 30 min before extubation (90 min); 2, from 30 min before until 30 min after extubation (60 min); 3, from 30 min until 2 h after extubation (90 min). ST segment changes indicating ischaemia were defined as a reversible ST segment depression of 2 mm or greater or an elevation of 3 mm or greater from baseline lasting for 1 min or more. During the study periods, heart rate, direct arterial pressure and arterial oxygen saturation by pulse oximetry were recorded.

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Table 1 Patient characteristics (mean (SD) or number). CPB, cardiopulmonary bypass; AXC, aortic cross clamp; IMA, internal mammary artery

	Ischaemic (n=14)	Non-ischaemic (n=38)	P
Age (yr)	55.1 (9.3)	56.7 (7.1)	ns
Sex (M/F)	11/3	33/5	ns
Weight (kg)	91.6 (13.2)	82.5 (12.3)	<0.05
CPB time (min)	67.5 (20.5)	57.2 (19.4)	ns
AXC time (min)	37.3 (12.9)	34.2 (12.7)	ns
IMA graft (Y/N)	12/2	33/5	ns
Extubation time (min)	290.8 (65.6)	231.1 (71.5)	<0.01
Inotrope (Y/N)	2/12	6/32	ns
Propofol sedation (Y/N)	2/12	8/30	ns

Statistical analysis was performed using SPSS for Windows, version 6.0. Patient characteristics were tested using *t* tests or the chi-square test as appropriate. ST segment data were analysed using paired *t* tests with Bonferroni correction. Haemodynamic data were analysed using analysis of variance. $P < 0.05$ was considered significant.

ST SEGMENT CHANGES

During the study period, 14 of 52 patients (26.9%) had ST segment changes indicating ischaemia. Patients were then assigned to one of two groups, ischaemic and non-ischaemic. The patient characteristics of the two groups are shown in table 1. There was no difference between the groups in age, sex distribution, duration of bypass or aortic cross clamp, use of an internal mammary graft, use of inotropic support or use of propofol sedation. Weight was higher and time to extubation longer in the ischaemic group. The duration of ischaemia in each time period is shown in table 2, and is presented as the ischaemic burden, that is, as min h^{-1} in each time period. The duration of ischaemia was significantly increased in periods 2 and 3 compared with period 1. However, the mean ST deviation (mm) showed no variation between the time periods.

HAEMODYNAMIC DATA

The mean heart rate was higher in patients who experienced ischaemia, and the difference between the groups was significant after extubation. Mean arterial pressure was not different between the two groups. In all patients arterial oxygen saturation was greater than 94%.

Table 2 Ischaemic time in min^{-1} for each period studied in the ischaemic group (patients who experienced myocardial ischaemia during extubation at different times after coronary artery surgery). See text for duration of periods

Patient	Period 1	Period 2	Period 3
1	50.67	55	60
2	0	14	18
3	16.67	10	1.33
4	20.67	60	60
5	36.67	53	60
6	34.67	58	60
7	2.67	25	42.67
8	20	35	48
9	0	0	1.33
10	48.67	59	57.33
11	34	60	60
12	0	7	27.33
13	0	0	1.33
14	4.67	59	57
Mean (SD)	19.24 (18.8)	35.36 (24.9)	39.61 (24.5)
P		<0.01	<0.001

Comment

This is a small observational study of ST segment changes occurring in patients during tracheal extubation within 6 h of coronary artery surgery. We selected this time period because we believe it reflects UK practice in patients who have undergone uncomplicated coronary artery surgery. It was not our intention to compare early and late tracheal extubation. We selected stringent criteria for ST segment change to reduce any effect of artefact.

In patients with coronary artery disease myocardial re-vascularization cannot always be complete; in many patients, it will not eliminate the potential for myocardial ischaemia. Edwards and co-workers demonstrated that not only tracheal intubation but also tracheal extubation is associated with myocardial ischaemia in general surgical patients. Patients extubated immediately after surgery may be haemodynamically unstable, fail to maintain their oxygen saturation or have inadequate analgesia, and all these factors have been implicated in precipitating myocardial ischaemia. The group of patients we observed after coronary artery surgery were well sedated and oxygenated and were haemodynamically stable before we attempted to wean them from positive pressure ventilation and extubate the trachea. We were mindful that ST segment changes in patients after coronary artery surgery are not always the result of myocardial ischaemia. They can occur in patients on digoxin, with ventricular hypertrophy, conduction abnormalities or post surgical pericarditis. To the best of our abilities we excluded such patients from our observations, on the basis of drug history and 12-lead ECG examination, so that the ST segment changes reported were likely to represent true myocardial ischaemia. In addition, we assessed the baseline ST segment before any attempt at weaning from positive pressure ventilation and change from baseline was analysed. This study demonstrates that there is a temporal relationship between tracheal extubation and myocardial ischaemia in patients after coronary artery surgery. Examination of the individual tracings showed that in 13 patients the ischaemic burden was increasing, and in one (patient 3) ST segment changes were resolving. However, the ST segment deviation did not increase.

Although it was not clinically apparent, we demonstrated the recognized association between a higher heart rate and myocardial ischaemia. We did not demonstrate an association between mean arterial pressure and myocardial ischaemia, perhaps because arterial pressure was actively controlled in these patients. In summary there is a temporal association between tracheal extubation and myocardial ischaemia in patients extubated within 6 h of coronary artery surgery. This is associated with a higher heart rate in these patients.

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Haemodynamic responses to extubation after cardiac surgery with and without continued sedation

J. CONTI, D. SMITH

Summary

We studied the haemodynamic response to cessation of mechanical ventilation and removal of the tracheal tube in 84 patients after coronary artery bypass grafting. Patients were sedated on the ICU with propofol 1–3 mg kg^{-1} h^{-1}, and randomly allocated to extubation while awake or while still sedated. Systolic and diastolic blood pressures and heart rate increased significantly faster in the awake group as mechanical ventilation was stopped; systolic blood pressure 6.1 (3.0) *vs* 0.7 (1.8) mm Hg min^{-1}, diastolic blood pressure 2.1 (1.6) *vs* 0.2 (0.9) mm Hg min^{-1}, heart rate 2.1 (1.7) *vs* 0.2 (0.5) beats min^{-2}; $P < 0.01$ in each case. Treatment was required for systolic hypertension during discontinuation of mechanical ventilation in 20 patients (53%) in the awake group and in three patients (7.5%) in the sedated group ($P < 0.001$). No patient in the sedated group had any new ischaemic ECG changes. Significant new ST segment changes did not occur in the sedated group but were present in five patients in the awake group ($P = 0.013$), one of whom suffered a perioperative myocardial infarction. Removal of the tracheal tube while patients are still sedated after coronary artery bypass grafting is safe, and reduces the incidences of haemodynamic disturbance and myocardial ischaemia during extubation. (*Br. J. Anaesth.* 1998; **80**: 834–836)

Keywords: intubation tracheal; extubation; cardiovascular responses; surgery cardiovascular

Avoidance of tachycardia and hypertension after coronary artery bypass graft (CABG) surgery is important for reducing postoperative morbidity and mortality.[1] After cardiac surgery, mechanical ventilation is usually discontinued and the tracheal tube removed when the patient is awake,[2 3] producing significant tachycardia and hypertension.[4–6] Esmolol may ablate these haemodynamic changes,[6] but at the dose required may have serious cardiovascular side effects. We investigated if removing the tracheal tube while patients are still sedated after CABG could safely reduce the haemodynamic response to extubation.

Methods and results

After obtaining approval from the Southampton Joint Ethics Committee and informed written consent, we studied 84 consecutive patients undergoing CABG over a 2-month period. All regular medications, except angiotensin-converting-enzyme inhibitors, diuretics and digoxin, were continued until the morning of surgery. Premedication was with oral lorazapam 1–3 mg 2 h before induction of anaesthesia, then morphine 5–10 mg and hyoscine 0.1–0.4 mg i.m. 1 h later.

Anaesthesia was induced with fentanyl 10 µg kg^{-1}, midazolam 2–5 mg or thiopentone 1–1.5 mg kg^{-1}, and pancuronium, and maintained with fentanyl to a total of 30–35 µg kg^{-1} and an infusion of propofol 1–3 mg kg^{-1} h^{-1}. Midazolam 4 mg was given at the start of cardiopulmonary bypass. A hypothermic bypass technique, with membrane oxygenator (Dideco D703) and arterial line filter, was used in all patients. Neuromuscular block was not antagonized at the end of surgery, and glyceryl trinitrate (GTN) 0.5 µg kg^{-1} min^{-1} was infused as a coronary vasodilator in most patients.

After surgery, patients were transferred to the cardiothoracic ICU where their lungs were ventilated, using a synchronized intermittent mandatory ventilation mode (Engstrom Erica) with 10 cm H_20 inspiratory assist. Systolic, diastolic and mean arterial blood pressures, central venous pressure, heart rate and nasopharyngeal temperature data were stored in the ICU monitors (PPG Hellige SMU612 or Mennen Horizon XL). A standard 5-lead ECG was used, with continuous computerized ST segment analysis in leads II and V5. We defined greater than 0.2 mV of new ST segment depression or greater than 0.3 mV of new ST segment elevation 60 ms after the J-point as a significant change.

On admission to the ICU patients were randomly allocated by a computer-generated sequence to removal of the tracheal tube while awake or while still sedated. During mechanical ventilation sedation was maintained with propofol 1–3 mg kg^{-1} h^{-1}. Adequate pain control was ensured with bolus doses of morphine 1–2 mg i.v. if required. Unless contraindicated by poor renal function or a history of gastrointestinal bleeding, patients received rectal diclofenac 100 mg and domperidone 30 mg at least 1 h before extubation. Systolic blood pressure was maintained at 90–130 mm Hg with infusions of GTN or inotropic agents as appropriate.

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Before discontinuing mechanical ventilation, the Pa_{CO_2} was adjusted to 4.5–5.5 kPa. The tracheal tube was removed when patients were warm (nasopharyngeal temperature >36°C), haemodynamically stable, with minimal blood loss and a Pa_{O_2} of >9.0 kPa on an FI_{O_2} <0.4. The propofol infusion was then adjusted to just obtund the eyelash reflex and each patient was allowed to stabilize at this level for a minimum of 10 min.

For patients in the awake group, the propofol infusion was stopped and patients allowed to wake up. During this time they were allowed to breathe via a Water's circuit giving manual assistance as necessary. The tracheal tube was removed when spontaneous respiratory efforts and gas exchange were satisfactory and patients were awake.

For those in the sedated group, the propofol infusion was continued while mechanical ventilation was stopped and the patients allowed to breathe via a Water's circuit giving manual assistance as necessary. When spontaneous respiratory efforts and gas exchange were satisfactory, the tracheal tube was removed and the propofol infusion stopped.

Just before extubation, the nasogastric tube was suctioned and removed. The mouth was cleared of secretions and a suction catheter passed down the tracheal tube, which was removed with the suction catheter *in situ*. Arterial blood gas analysis was performed before cessation of mechanical ventilation and 20 min after extubation.

Hypertension was treated by increasing the infusion rate of GTN. If the systolic blood pressure was >150 mm Hg a bolus dose of GTN 1 mg was given, and the infusion rate of GTN further increased. A second bolus of GTN was given if required 2 min later. We looked for changes from a baseline value taken 10 min before cessation of mechanical ventilation in the heart rate, systolic (SBP) and diastolic (DBP) blood pressures. Data were analysed by linear regression to measure the rate of increase of all haemodynamic variables (heart rate, SBP, DBP) from cessation of mechanical ventilation until removal of the tracheal tube, to take into consideration the different duration of recovery of spontaneous ventilation for individual patients. An unequal variance t-test was then performed using SPSS for Windows (version 6.1). Baseline corrected t-testing was performed at set time points as used previously,[4] with statistical significance assumed at $P < 0.01$. Non-parametric data were analysed using the chi-square test, assuming statistical significance at $P < 0.05$.

Data were collected on 79 of the 84 patients who were enrolled in the study. Five patients were excluded because of major surgical or postoperative complications. One further patient in the awake group was excluded because the propofol was stopped several hours before extubation and the patient was extremely slow to waken. A total of 38 patients were managed according to the study procedure in the awake group and 40 patients in the sedated group.

There were no differences between the two groups in patient characteristics, including age, body mass index, history of hypertension, left ventricular ejection fraction, previous myocardial infarction, preoperative drug history and mean time to removal of the tracheal tube (441 min *vs* 448 min, overall range 175–1173 min). One patient in the awake group received morphine before removal of the tracheal tube, but no patient woke with severe pain.

Mean (range) infusion rates of propofol before weaning were 1.84 (0–3.2) mg $kg^{-1}h^{-1}$ for patients in the awake group and 1.64 (0.5–3.0) mg $kg^{-1}h^{-1}$ for patients in the sedated group. The mean (range) duration of weaning was 7.44 (5–18) min for patients in the awake group and 7.25 (5–24) min for patients in the sedated group. For patients in the awake group, the mean time from stopping the propofol infusion to extubation was 14.1 (6–38) min. There were no significant differences between groups in blood gas analysis before or after extubation; the mean (range) arterial P_{CO_2} after removal of the tracheal tube was 5.3 (4.1–6.5) kPa for patients extubated awake and 5.4 (4.2–7.1) kPa for patients extubated while sedated.

Haemodynamic data during cessation of mechanical ventilation and extubation are illustrated in fig. 1. There were no significant differences between the groups in baseline values for any haemodynamic variable. Systolic and diastolic blood pressures and heart rate increased significantly faster in the awake group during cessation of mechanical ventilation: systolic blood pressure 6.1 (3.0) *vs* 0.7 (1.8) mm Hg

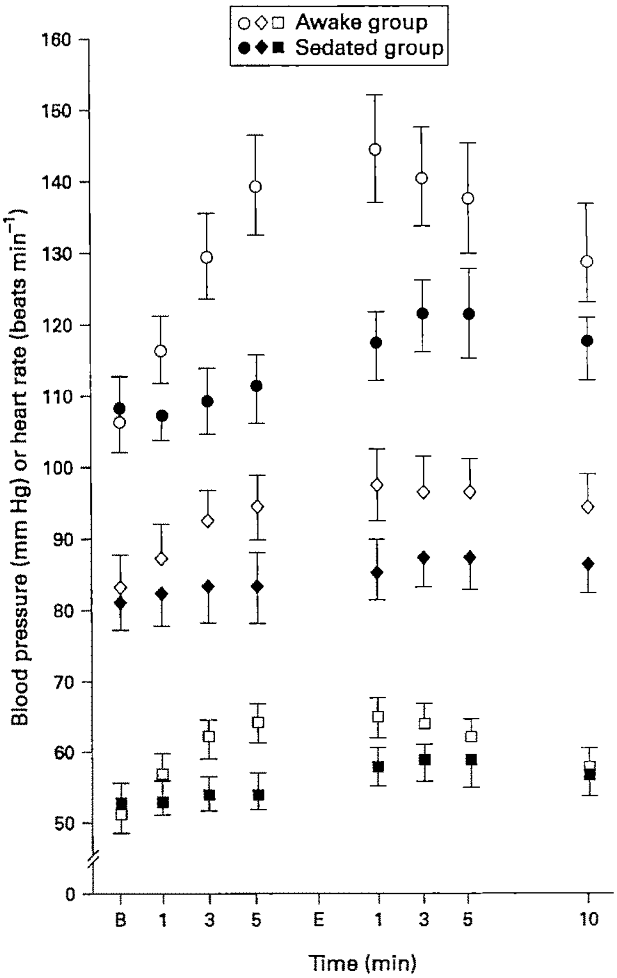

Figure 1 Changes in systolic blood pressure (circles), diastolic blood pressure (squares) and heart rate (diamonds) during cessation of mechanical ventilation and removal of the tracheal tube while sedated or awake. Time (min) is from cessation of mechanical ventilation or removal of the tracheal tube; B = baseline measurement before cessation of mechanical ventilation, E = extubation.

min^{-1}, diastolic blood pressure 2.1 (1.6) *vs* 0.2 (0.9) mm Hg min^{-1}, heart rate 2.1 (1.7) *vs* 0.2 (0.5) beats min^{-2}; $P < 0.01$ in each case. Not all patients in the awake group had haemodynamic changes associated with cessation of mechanical ventilation, but two patients developed ischaemic ECG changes with only modest increases in heart rate and systolic pressure. After removal of the tracheal tube, there was a further non-significant increase in all haemodynamic variables in both groups; the differences from baseline for all variables except diastolic blood pressure ($P = 0.11$) were still significant at 10 min after extubation.

No patients required treatment for systolic hypertension before mechanical ventilation was stopped. However, treatment was required during cessation of mechanical ventilation in 20 patients (53%) in the awake group and in three patients (7.5%) in the sedated group ($P < 0.001$). Long-term β-blocker therapy before operation had no influence on the need for antihypertensive treatment.

The ST segment was interpretable in 26 of the 38 patients in the awake group and 28 of the 40 patients in the sedated group. No patient in the sedated group had any new ischaemic ECG changes. Significant new ST segment changes occurred in five patients in the awake group ($P = 0.013$) and lasted for 1–5 min; in one of these patients there was already ECG evidence of ischaemia before mechanical ventilation was stopped. In all five patients, the ST segment changes were associated with significant increases in heart rate or systolic pressure or both, in three cases to >40% above baseline. One patient with new ischaemic changes suffered a perioperative myocardial infarction.

Comment

The incidences of haemodynamic disturbance and new ischaemic ECG changes in patients in whom mechanical ventilation was stopped and the tracheal tube removed while they were awake are in keeping with those in other studies of patients undergoing cardiac surgery[4–6]; both incidences are markedly reduced by removing the tracheal tube while patients are sedated. We encountered no problems with the airway or respiration in the sedated group, and no patients required reinsertion of the tracheal tube. The low use of opioids and incidence of pain on waking from propofol infusion in patients undergoing cardiac surgery has been commented on before.[7] Several authorities[2 3] state that patients should awaken before extubation so that their neurological status can be assessed. However, we have not found this to be necessary; waking while intubated is stressful and has risks other than haemodynamic compromise.[7]

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Intra-articular injection of ketorolac in the rat knee joint: effect on articular cartilage and synovium

M. G. IRWIN, K. M. C. CHEUNG, J. M. NICHOLLS, N. THOMPSON

Summary

We have investigated the effects of intra-articular (i.a.) administration of ketorolac in the rat knee joint. Thirty Sprague–Dawley rats were given 0.25 ml of a standard preparation of ketorolac trometamol (10 mg ml^{-1}) by injection into the right knee joint and 0.25 ml of 0.9% physiological saline solution by injection into the left knee as a control. Ten rats were killed at 24 h, 10 at 48 h and 10 at 5 days after injection. The joints were prepared and sectioned for histological examination. There was significantly more inflammation in those knees that had received i.a. ketorolac at all times of examination, with the most severe changes occurring 5 days after injection. A further group of 10 rats were given 0.25 ml of 10% w/v ethanol in physiological saline (similar to the vehicle for parenteral ketorolac) injected into the knee joint, with a 0.9% saline control injected in the other knee. These rats were then killed at 5 days (as this was the time interval after which we found the maximum inflammatory response in the earlier phase of our study). The joints were prepared and examined histologically. We feel that the absence of inflammatory changes in these joints make it unlikely that ethanol was responsible for the inflammation produced by ketorolac injection. (*Br. J. Anaesth.* 1998; **80**: 837–839)

Keywords: analgesics non-opioid ketorolac; analgesia intra-articular; rat

Intra-articular injection of local anaesthetic drugs or opioids or both is commonly used to manage pain after arthroscopic knee surgery, although opioids have been inconsistent in their efficacy. Ketorolac, a powerful analgesic agent of the non-steroidal, anti-inflammatory class (NSAID), inhibits the cyclo-oxygenase enzyme system and hence prostaglandin synthesis. It has been shown to be an effective non-opioid analgesic for this type of surgery when given systemically, reducing pain and joint swelling.[1] There are, however, several well documented side effects associated with the use of NSAIDs, particularly at higher dosages. This has prompted the manufacturer of ketorolac, Syntex Pharmaceuticals, in conjunction with the Committee on Safety of Medicines,[2] to recommend a lower dose regimen for the drug that may not be quite as efficacious.[3] It is interesting to speculate that ketorolac may be at least as effective if administered directly to the site of tissue trauma, producing higher local tissue concentrations and less risk of systemic upset.[4 5] Although it is approved for i.v., i.m. and oral use, no toxicological data exist regarding i.a. administration. Using the knee joint of rats, we investigated ketorolac's effects on synovium and articular cartilage after direct injection.

Methods and results

Approval for the study was obtained from the University of Hong Kong Committee on the Use of Live Animals in Teaching and Research. Thirty mature Sprague–Dawley rats each weighing 250–300 g were anaesthetized using 35 mg kg^{-1} of intraperitoneal phenobarbital. Under aseptic conditions, 0.25 ml of a standard preparation of ketorolac trometamol (10 mg ml^{-1}), which also contains ethanol (10% w/v), sodium chloride and water, was injected into the right knee joint and 0.25 ml of physiological 0.9% saline into the left. The animals were then allowed to awaken and were returned to their cages.

The rats were killed by a lethal injection of phenobarbital, 10 at 24 h, 10 at 48 h and 10 at 5 days after drug administration. The knee joints were detached and examined for gross signs of haematoma. They were labelled (left/right and time of death), then placed in 10% neutral buffered formalin for 2 weeks. The joints were then decalcified in 14% EDTA for another 3 weeks, when they were embedded in paraffin and processed for sectioning. Sectioning was carried out at 5 µm intervals and the resulting slide preparations stained with haematoxylin and eosin. The same pathologist (JN) examined all the slides and was blinded to the injectate used in each joint.

Inflammatory changes in the joints were classified as follows:

1 = No inflammation;

2 = Minimal inflammation (mild congestion and oedema);

3 =Mild inflammation (congestion and oedema, small number of neutrophils);

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Table 1 Incidence and severity of knee joint inflammation (5 = most severe). *P* value is the probability of between-group differences being attributable to chance

	Control group Inflammation					Ketorolac group Inflammation				
	1	2	3	4	5	1	2	3	4	5
Time after injection										
24 h (P=0.034)	7	3	0	0	0	2	6	2	0	0
48 h (P=0.0458)	7	3	0	0	0	1	4	3	2	0
5 days (P=0.0029)	6	0	4	0	0	0	0	1	0	9

4 = Moderate inflammation (neutrophils and macrophages, synoviocyte hyperplasia);

5 = Severe inflammation (neutrophils and macrophages, synoviocyte hyperplasia, fibrin exudation).

The Mann–Whitney U test was used to calculate the probability of the differences between the experimental and control groups at 24 h, 48 h and 5 days being attributable to chance. $P < 0.05$ was taken as significant.

The incidence of haematoma over the joint capsule on gross examination was (control:ketorolac) 0:1 at 24 h, 2:2 at 48 h and 0:1 at 5 days after injection. All haematomata were small and the difference was not statistically significant.

The degree of histological inflammatory change in each group is shown in table 1. There was significantly more inflammation in those knees which had received i.a. ketorolac at all times of examination, with the most severe changes occurring 5 days after injection (fig. 1).

In the light of these results, we decided to investigate the possible role of the drug vehicle in producing these inflammatory changes. We studied a further group of 10 rats, and injected 0.25 ml of a solution of 10% w/v of ethanol in physiological saline (similar to the vehicle for parenteral ketorolac) into one knee joint of each animal. An equal volume of plain 0.9% saline solution was injected into the opposite knee as a control. These rats were killed at 5 days after injection, as this was the time interval at which we found the maximum inflammatory response in the earlier phase of our study. The joints were prepared and examined histologically as before. All these joints showed no or minimal inflammation (fig. 2), although one in the ethanol group had signs of acute septic arthritis.

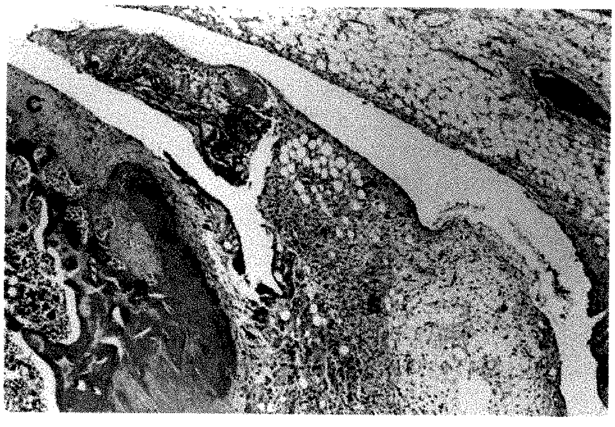

Figure 1 Knee joint of rat 5 days after injection of ketorolac, showing bone (B), cartilage (C) and synovium (S). Note the marked inflammation, with fibrinous exudate. Haematoxylin and eosin stain, × 80.

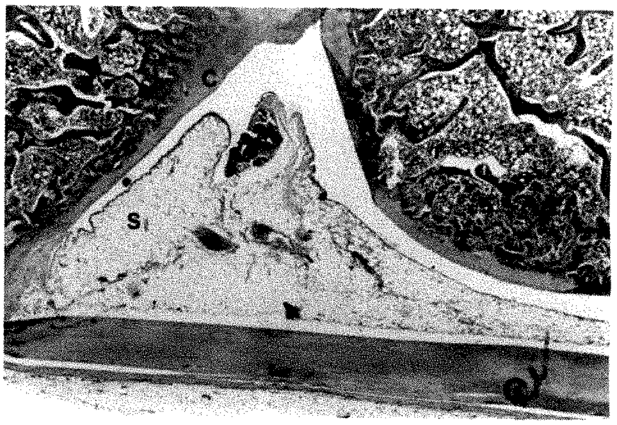

Figure 2 Knee joint of rat 5 days after injection of ethanol 10% w/v, showing bone (B), cartilage (C) and synovium (S). The synovium shows minimal inflammation. Haematoxylin and eosin stain, × 80.

Discussion

Although the mode of action and chemical type of different NSAIDs varies significantly, ketorolac is the only parenteral preparation that has a product license for i.v. administration. It also appears to cause less pain on injection. This would suggest that it is less irritant to tissue than other parenterally administered NSAIDs, although *in vitro* studies investigating cartilage metabolism and proteoglycan synthesis have shown that different NSAIDs have different effects,[6,7] and it has been suggested that ketorolac is not the most suitable agent for i.a. use.[8] Ketorolac is not licensed by the United States Food and Drug Administration for i.a. use and the manufacturer was unable to provide any animal toxicological data regarding such administration. However, there has been interest in i.a. use of ketorolac in humans. Monahan and colleagues compared 60 mg of ketorolac in 30 ml saline with 30 ml of 0.25% bupivacaine instilled into the knee joint after arthroscopy, and found that visual analogue pain scores were lower in the immediate postoperative period with bupivacaine but did not differ significantly between the groups over the following 5 days.[9] In another study, Reuben and Connelly concluded that 60 mg of i.a. ketorolac improved comfort in the early postoperative period in patients undergoing knee arthroscopy, especially when combined with i.a. bupivacaine, and provided better analgesia compared with i.a. bupivacaine alone.[4] In another investigation these workers showed that i.a. ketorolac produces comparable analgesia to that achieved with i.a. morphine, with no benefit when given in combination.[10]

Although these results are interesting, and suggest a potential new application for NSAIDs, there are concerns about exposing patients to the use of a drug in an area where there is little evidence to suggest that it is safe in the short or long term.[8,11,12] It is important to consider the ethical, legal and financial consequences of a patient developing a complication of i.a. ketorolac in this context.

We have shown in this animal study that a relatively high local dose of a standard preparation of ketorolac causes severe synovial inflammation that is not seen in control joints injected with saline. This would appear to be a local effect, because the rats' opposite knee joints were used as the controls. It is interesting also that the maximal inflammatory response was seen at 5 days after injection. As most arthroscopic surgery is performed as a day-stay procedure, this is beyond the observation period in the human studies where out-of-hospital data have been collected by questionnaire or telephone follow-up without joint examination or biopsy.

The control solution for injection did not contain ethanol, which is present in 10% weight by volume (w/v) in the parenteral ketorolac preparation used, as we wished to assess the direct effects of the preparation rather than just ketorolac itself. We have been unable to find any scientific literature on the effects of direct application of ethanol to synovial tissue, so we investigated its effects in the second phase of our study. We feel that the lack of changes in joints injected with ethanol makes it unlikely that ethanol is responsible for the inflammation found earlier.

Joint changes in rats may not, of course, be directly comparable to those found in humans. It is not possible to make a direct comparison without investigating humans. However, the Sprague–Dawley rat has often been used as a convenient animal model for toxicology studies. We can only surmise that, if such significant synovitis is produced in rats, it may well occur in other animals. There is a need for caution when contemplating i.a. administration of ketorolac in humans.

A longer study may have shown a natural regression of the degree of inflammation. However, we consider that the degree of inflammation found at 5 days is relevant to the clinical situation, and that our findings are important because they question both the suitability of this route of administration for the currently available parenteral ketorolac preparation, and the ethics of performing such studies on human subjects without appropriate toxicological data.

Although the systemic and *in vitro* effects of NSAIDs have been extensively studied, we feel that our results indicate that more attention should be paid to the toxicology of i.a. ketorolac administration before its widespread clinical use.

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British Journal of Anaesthesia 1998; **80**: 840–842

Halothane increases the open probability of glycine-activated channel current in rat central neurones

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Summary

Glycine-activated single-channel currents in rat central neurones were recorded using the outside-out mode of the patch-clamp technique. The unitary conductance of the current was 21 pS. The current evoked by 10 µM glycine had a mean burst duration of 47.8 (2.6) ms and open probability of 0.09 (0.016). Halothane (1 mM) increased the open probability to 0.19 (0.03) without changing either unitary conductance or burst duration. These results suggest that halothane increased the open probability via an increase in the affinity of the receptor for the agonist. Potentiation of the glycine response may reduce excitability of postsynaptic neurones and may contribute to general anaesthesia produced by volatile agents. (*Br. J. Anaesth.* 1998; **80**: 840–842)

Keywords: anaesthetics volatile halothane; channels neurotransmitter-activated; rat; receptors amino acid; theories of anaesthetic action lipid bilayer

Volatile anaesthetics at clinical concentrations affect the efficacy of neurotransmitter-activated channels and modify the transmission at synapses in the central nervous system; these actions may contribute to production of the state of anaesthesia in humans and in animals.[1] Excitatory postsynaptic responses, such as muscle and neuronal nicotinic acetylcholine responses[2,3] and glutamate responses,[4] are reduced by volatile anaesthetics. Inhibitory amino acid responses, namely, the γ-aminobutyric acid (GABA)- or glycine-induced chloride currents are augmented by these agents.[4] The glycine receptor belongs to a superfamily of fast neurotransmitter-gated receptor channels and glycine is the major inhibitory transmitter in the spinal cord and brain stem. In a review by Betz the existence of glycine receptors in many higher brain regions, such as cerebral cortex, hippocampus, thalamus, colliculi and brain stem[5] has been described. Single-channel data are not available for the effects of volatile anaesthetics on the glycine-activated channel, although the effects of these agents on acetylcholine-activated channels and GABA-activated channels have been extensively examined at the single-channel level.[2,6] In the present study we examined the effects of halothane on glycine-activated single-channel currents in outside-out membrane patches of rat central neurones and showed that halothane increased the open probability of the channel without changing unitary conductance.

Methods and results

Wistar rats (12 to 18 days old) were decapitated under ether anaesthesia and transverse slices of the brain stem cut to a thickness of 350 µm using a microslicer (DSK, model DTK-1000, Japan). The slices were incubated in a normal external solution containing 10 000 U ml^{-1} Dispase (Godo Shusei Co. Ltd, Japan) for 1 h at 31°C. Thereafter, the nucleus tractus solitarius was micropunched from the slices and the neurones dissociated mechanically with a fire-polished Pasteur pipette. Dissociated neurons adhered to the bottom of the culture dish (Falcon 3801, Japan) within 1 h. We used neurons with dendritic processes in all experiments. The ionic composition of the external solution was (in mM): NaCl 150, KCl 5, $MgCl_2$ 1, $CaCl_2$ 2, glucose 10, N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) 10. The pH was adjusted to 7.4 with Tris (hydroxymethyl) aminomethane base (Tris-base). The intrapipette solution was composed of (in mM): K-gluconate 70, KCl 50, NaCl 30, $MgCl_2$ 1, ATP Mg 2, $CaCl_2$ 0.5, ethylene glycol-bis (-aminoethylether)-N,N,N',N-tetraacetic acid (EGTA) 5, HEPES 10. The pH was adjusted to 7.2 with Tris-base. The Cl^- concentration in the external and intrapipette solutions was 161 and 83 mM, respectively, and the activity 125 and 61 mM; these were measured with an F1012Cl Cl^- electrode connected to an ION 85 Analyser (Radiometer A/S, Copenhagen, Denmark) at 25°C in a black beaker. From the Cl^- activities, the equilibrium potential for Cl^- is calculated to be −18 mV. Electrical recordings were performed using the outside-out configuration of the patch-clamp technique, using a patch-clamp amplifier (EPC 7, List Medical, Germany). The resistance of the circuit between the recording electrode filled with the intrapipette solution and the reference electrode was 4–8 MΩ. Current and voltage were monitored on a storage oscilloscope (R5113, Tektronix, USA) and recorded with a pen-recorder. Glycine and halothane were applied to the external surface of the membrane patch using the "Y-tube" method.[4] Drugs were directly dissolved in the external solution just

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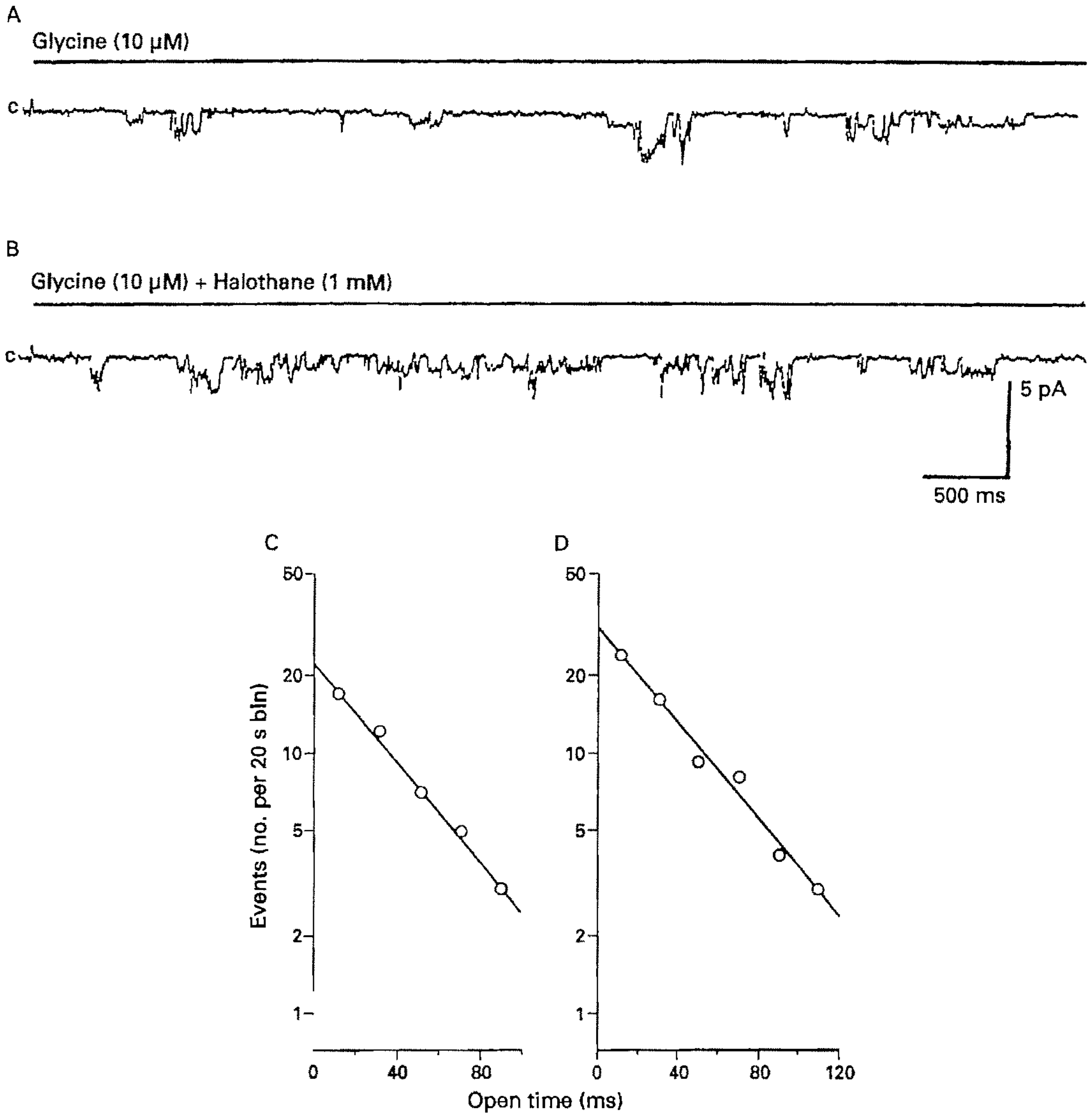

Figure 1 Increase in open probability of the glycine-activated channel by halothane. (A) Glycine (10 μM) was applied to the external surface of the outside-out membrane patch, which was voltage-clamped at −60 mV Glycine induced single-channel currents with a conductance of about 21 pS. Assuming four channels in the patch, the open probability was estimated to be 0.07. (B) Simultaneously applied halothane (1 mM) increased the open probability to 0.14 without altering the unit amplitude of the current. From the same patch as in (A) The closed channel level is indicated by "C" at the left-hand end of the record; downward deflection of the trace represents the inward current. (C) Open time histogram obtained from the record in (A) plotted in semi-logarithmic scale. With a cut-off frequency of about 100 Hz of the paper record, the open time is equivalent to the burst duration. The slope of the solid line gives the mean burst duration, which was 46 ms in the control. (D) Open time histogram in the presence of halothane (1 mM; obtained from (B)) yields a mean burst duration of 47 ms.

before use. Commercially available halothane is stabilized by adding thymol at 0.01%. To obtain a halothane concentration of 1 mM at room temperature, 0.13 μM thymol is required. Thymol itself at this concentration did not affect the current as reported previously.[4] All experiments were performed at room temperature (23–25°C).

Before making an outside-out patch, the neurone was voltage-clamped at −60 mV in the whole cell mode and glycine applied to check the presence of the glycine receptor–chloride channel complex in the cell membrane. After formation of an outside-out membrane patch, the intrapipette potential was held at −60 mV throughout and 10 μM of glycine was perfused onto the external surface of the membrane. Glycine evoked single-channel currents with a unitary amplitude of 0.9 pA (fig. 1A). The average amplitude with five patches was 0.9 (0.1) pA (mean (SD)). This amplitude and the driving force of 42 mV (60–18 mV) allow an estimation of the single-channel conductance of about 21 pS, which lies in the reported range of conductance in cell-attached patches for cultured spinal neurones.[7] Halothane markedly increased the opening of the channel, without affecting the unit amplitude (fig. 1B). Assuming four channels in the patch in fig. 1 (four channels were open simultaneously), the open probability was 0.07 in the control. Halothane increased the open probability to 0.14 (fig. 1B). In five experiments, the open probability was increased significantly from 0.09 (0.016) to 0.19 (0.03) by 1 mM halothane (Student's *t*-test; $P < 0.01$).

In the present study, we used paper records with a cut-off frequency of about 100 Hz. The open time, therefore, means the burst duration of the opening. Figure 1C and fig. 1D illustrate the burst duration histogram with a bin width of 20 ms. In the control, the mean burst duration was 46 ms, which was not changed by halothane (1 mM). With five patches, the mean burst duration was 47.8 (2.6) ms in the control. Halothane did not affect the burst duration (49.5 (2.9) ms), reflecting an increased frequency of bursting.

Comment

We have shown for the first time at the single-channel level that a volatile anaesthetic, halothane, increased the open probability of the glycine-activated channel without changing the unitary conductance. Although new volatile anaesthetics, such as isoflurane, sevoflurane and desflurane, have been successfully used in clinical practice in recent years, halothane still seems to be considered as a model volatile anaesthetic. The concentration of halothane used in the present study (1 mM) is higher than that attained at minimum alveolar concentration (MAC) for the agent. In whole-cell experiments with dissociated neurones, the chloride current induced by 20 μM glycine was increased by halothane in a dose-dependent manner up to 2.7 fold (at 2 mM),[4] and in the present study the open probability was doubled. It may, therefore, be reasonable to suggest that halothane around MAC increases the open probability of the channel.

The consistency of the burst duration is in accordance with the idea that halothane increased the affinity of the glycine receptor for the agonist. This notion is supported by the parallel leftward shift of the glycine concentration–response curve of the whole-cell current that was described in dissociated rat central neurones and in recombinant glycine receptors.[4 8] A similar action of diazepam on the $GABA_A$ receptor, reported by Twyman and colleagues, showed that diazepam made the GABA-evoked burst more frequent without changing its duration.[9] The authors further described that phenobarbital prolonged the burst duration without altering the frequency, thereby suggesting that phenobarbital stabilized the open burst state via binding to a different modulatory site at or near the chloride channel. For the interaction of halothane with the GABA receptor-chloride channel complex, Yeh and colleagues suggested that halothane affected the gating mechanism of the channel, on the basis of the finding that the anaesthetic at 4 MAC increased the burst duration and the open probability of the channel in cultured dorsal root ganglion neurones of the rat.[6]

In conclusion, the present single-channel data show that the open probability of the glycine-activated channel of rat central neurones is potentiated by halothane, which may result from an increase in the affinity of the receptor for the agonist.

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CASE REPORTS

Ropivacaine-induced seizure after extradural anaesthesia

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Summary

Ropivacaine is considered safer than bupivacaine, on the basis of experimental and human data that indicate a lower systemic toxicity. Here we report the occurrence of a single seizure after i.v. administration of ropivacaine 120 mg intended for extradural block in a patient having postpartum tubal ligation. The only prodromal symptom was nervousness, and the only cardiovascular manifestation was sinus tachycardia. Systemic toxicity, although less than that expected with bupivacaine, can occur with ropivacaine. (*Br. J. Anaesth.* 1998; **80**: 843–844)

Keywords: anaesthetics local ropivacaine; ropivacaine toxicity; anaesthesia obstetric

Ropivacaine is an amide-type local anaesthetic agent that is prepared as an S-isomer. Previous studies showed the relative neuro- and cardiovascular safety of ropivacaine compared with bupivacaine.[1 2] Here we report a case of systemic toxicity after extradural anaesthesia with ropivacaine. To our knowledge, this is the first reported case of systemic toxicity after attempted extradural block using ropivacaine.

Case report

On April 21, 1997, a 23-year-old woman (G4 P3, 59 kg, ASA I) was to undergo postpartum tubal ligation. On the evening before the procedure, a lumbar extradural catheter with a closed end and two side holes was placed for labour pain. Aspiration was negative for cerebrospinal fluid and blood. Examination revealed full cervical dilatation, so no local anaesthetic was injected. After a normal vaginal delivery, the extradural catheter was left in place in anticipation of the tubal ligation.

Next morning, anaesthesia for postpartum tubal ligation was discussed with and accepted by the patient. Monitoring included pulse oximetry, non-invasive arterial pressure and electrocardiogram (ECG). After negative aspiration for blood and cerebrospinal fluid, 0.75% ropivacaine was injected extradurally in fractionated doses. Initially, a 2-ml bolus was given (15 mg). Three min later, there were no signs of subarachnoid block; ropivacaine 4 ml (30 mg) was therefore injected. No changes in the patient's status were detected and another 4 ml (30 mg) was injected, combined with fentanyl 100 μg. After a second negative aspiration, another 4 ml (30 ml) was given. There were no signs or symptoms suggestive of intravascular injection, such as altered consciousness, blurred vision, ringing in the ears or metallic taste. Administration of an additional 4 ml was then attempted, but after injection of only 2 ml (15 mg), the patient closed her eyes and stated that she felt nervous; no further drug was given. The total dose of ropivacaine was 120 mg injected in increments over a period of 11 min. Within a few seconds of injection of the last increment, the patient experienced a generalized tonic–clonic seizure lasting approximately 1 min. During this episode the patient maintained her airway and, apart from sinus tachycardia of 120 beats min^{-1} (as proven by ECG), there were no other arrhythmias. Arterial pressure was 115/70 mm Hg, and oxygen saturation 100%. The patient spontaneously recovered before medical intervention but was lethargic. Apart from minor injury to the edges of the tongue, there were no injuries nor neurological, respiratory or cardiovascular sequelae. No sensory or motor effects developed subsequent to the local anaesthetic injection. The procedure was cancelled. Inspection of the extradural catheter after removing the opaque adhesive tape revealed blood in the distal portion.

The next day the patient was discharged home. She was readmitted a few days later, had tubal ligation under spinal anaesthesia, and made an uneventful recovery.

Discussion

Ropivacaine is a relatively new amide local anaesthetic agent that is commercially prepared as a pure S-enantiomer.[1–4] Experimental data have shown that ropivacaine is less cardio- and neurotoxic than racemic bupivacaine.[1–6] Central nervous system toxicity after accidental i.v. administration of local anaesthetics has been reported before.[7 8] However, only one case of convulsion was reported with ropivacaine after transarterial brachial plexus block.[9] Various techniques have been advocated to reduce the unintentional i.v. injection of local anaesthetics during extradural analgesia; none has been shown to be infallible.[10–12]

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In the case reported here, the serum drug concentration was not determined. However, the absence of a history of any illness, especially epilepsy or pre-eclampsia, the nonrecurrence of the convulsions, the absence of motor and sensory block, and the timing of the convulsion in relation to the local anaesthetic injection were suggestive of a toxic reaction to the drug.

In studies using intravenous ropivacaine and bupivacaine on human volunteers, there was a clear difference between the two drugs with regard to their ability to induce signs and symptoms of central nervous system (CNS) toxicity.[1 2] Although the early symptoms of CNS toxicity were similar with both drugs, they appeared more often, occurred earlier, at a lower dose and at a lower arterial and venous plasma concentration with bupivacaine.[1 2] I.v. infusion of ropivacaine was well tolerated and without prodromal CNS symptoms in seven of 12 volunteers, in spite of the intravenous infusion of 150 mg in 15 min.[1] Our patient developed a convulsion with only one prodromal symptom, namely nervousness, at a dose of 120 mg injected intermittently over 11 min.

The absence of classic symptoms of CNS toxicity in spite a large dose of ropivacaine may indicate a better tolerance of ropivacaine, but it takes away the warning signs of imminent convulsions. It may therefore be prudent to add a reliable agent that acts as a marker for unintentional intravenous administration, such as epinephrine.[13] Another alternative may be to use as a marker lidocaine, which readily elicits prodromal symptoms without adverse cardiovascular effects. In addition, fractionation of the total dose, although it did not alert us to the position of the extradural catheter, is important because it limits the systemic toxicity of local anaesthetics.

There are various possible reasons for failure to detect the intravascular position of the catheter. The catheter could have been against a blood vessel wall; a blood clot in the terminal part of the catheter might have acted as a one-way valve; and the opaque tape could have prevented the detection of blood in the distal portion of the catheter.

In conclusion, this case report demonstrates the relative absence of prodromal symptoms of CNS toxicity after i.v. injection of a relatively large dose of ropivacaine and the absence of serious manifestations of cardiovascular toxicity. It emphasizes the importance of fractionating the total dose of a local anaesthetic, as this prevents a major reaction in the event of i.v. injection. It also highlights the value of using a marker to detect intravascular injection.

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British Journal of Anaesthesia 1998; **80**: 845–847

Co-incidental diagnosis of an extradural abscess while siting an extradural catheter for postoperative analgesia

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Summary

Extradural abscess is a rare but serious complication of the extradural route of administration of analgesic drugs. We report a case of spontaneous extradural abscess diagnosed during placement of an extradural catheter for analgesia after a negative diagnostic laparotomy. Magnetic resonance imaging is the usual diagnostic tool of choice. This, and subsequent surgery, confirmed the diagnosis suspected after drainage of pus through the Tuohy needle. (*Br. J. Anaesth.* 1998; **80**: 845–847)

Keywords: analgesic techniques extradural; complications extradural abscess

Neurological damage is a rare complication after insertion of an extradural catheter. One mechanism is inadvertent introduction of infection into the extradural space with subsequent abscess formation, first reported in 1974.[1] The quoted incidence of abscess formation accompanying extradural catheterization in the obstetric population is 1 in 505 000.[2] This is an order of magnitude less than the incidence quoted for spontaneous abscess in the hospital population as a whole of 0.2–1.2 per 10 000 admissions.[3]

We present a case of extradural abscess diagnosed during routine siting of an extradural catheter for analgesia after laparotomy, when pus exuded from the Tuohy needle upon entry of the extradural space. To our knowledge this case is unique.

Case report

A 76-year-old woman, weighing 84 kg and previously fit and well, was referred to a consultant physician with a 1-month history of polyuria and polydipsia, and non-specific bilateral loin pain of 2 weeks' duration. She had lost 25 kg in weight over the preceding 6 months. Examination revealed an obese woman with a pyrexia of 38°C, who was clinically in atrial fibrillation with a ventricular rate of 150 beats min^{-1}. Arterial pressure was within normal limits. A soft mid-systolic murmur could be auscultated in the mitral region. She was tachypnoeic (22 breaths min^{-1}), with decreased breath sounds at the base of the left lung. Examination of the abdominal and thoracolumbar spine was unremarkable, although hindered by her size. Neurological examination was normal, with full power in both legs. Investigations of note were as follows: serum glucose 26 mmol l^{-1}, white cell count 20.1 × 10^{9} l^{-1} (predominantly neutrophils), alkaline phosphatase 216 units l^{-1}, C-reactive protein 470 mg l^{-1}. Amylase was within the normal range. Arterial blood gas analysis showed pH = 7.41, Pa_{O_2} = 87 mm Hg, Pa_{CO_2} = 25 mm Hg and a base deficit of 7.3 mmol l^{-1} on 5 l min^{-1} of oxygen by facemask. Her ECG confirmed atrial fibrillation with bifascicular block. A transthoracic echocardiogram showed no valvular vegetations. A chest radiograph confirmed left basal shadowing and thoracolumbar spine radiographs revealed only mild osteoporosis. Three sets of venous blood cultures were taken during the admission period.

The initial diagnosis was diabetes mellitus, presenting in atrial fibrillation, with a presumed left basal chest infection. Immediate management consisted of continued facemask oxygen, oral trimethoprim, oral digoxin, an i.v. infusion of insulin according to a sliding scale and s.c. heparin. By day 2 after admission, the patient's heart rate had reverted to sinus rhythm and she was started on maintenance oral amiodarone therapy. However, the pyrexia persisted, and all three sets of venous blood cultures grew *Staphylococcus aureus* sensitive to flucloxacillin. Concurrently, her abdomen became acutely distended, and plain radiographs showed dilated loops of large bowel. An abdominal ultrasound scan contributed no further diagnostic information, and urinalysis was negative. Her antibiotics were changed from oral trimethoprim to i.v. flucloxacillin 1 g four times daily, and after surgical review the patient was listed for laparotomy the following day (day 3), on the assumption that the source of sepsis was intra-abdominal.

There were no complications during general anaesthesia for the procedure, which lasted for 2 h. No intra-abdominal abnormalities were found other than dilated loops of sigmoid colon. A diagnosis of pseudo-obstruction was therefore postulated. In view of the difficulties likely to be encountered by an elderly, obese patient recovering from general anaesthesia and abdominal surgery, she was admitted to the ICU for overnight ventilation. A clotting screen was normal, so extradural analgesia was provided. The patient was placed in the left lateral position, and extradural catheterization attempted at T10–11, under aseptic conditions using a 16 gauge Tuohy needle and the technique of loss of resistance to air. Using a midline approach, the fibrous resistance of the ligamentum flavum was encountered at a depth of 5 cm. Further advancement of the needle resulted in a clear loss of resistance to air,

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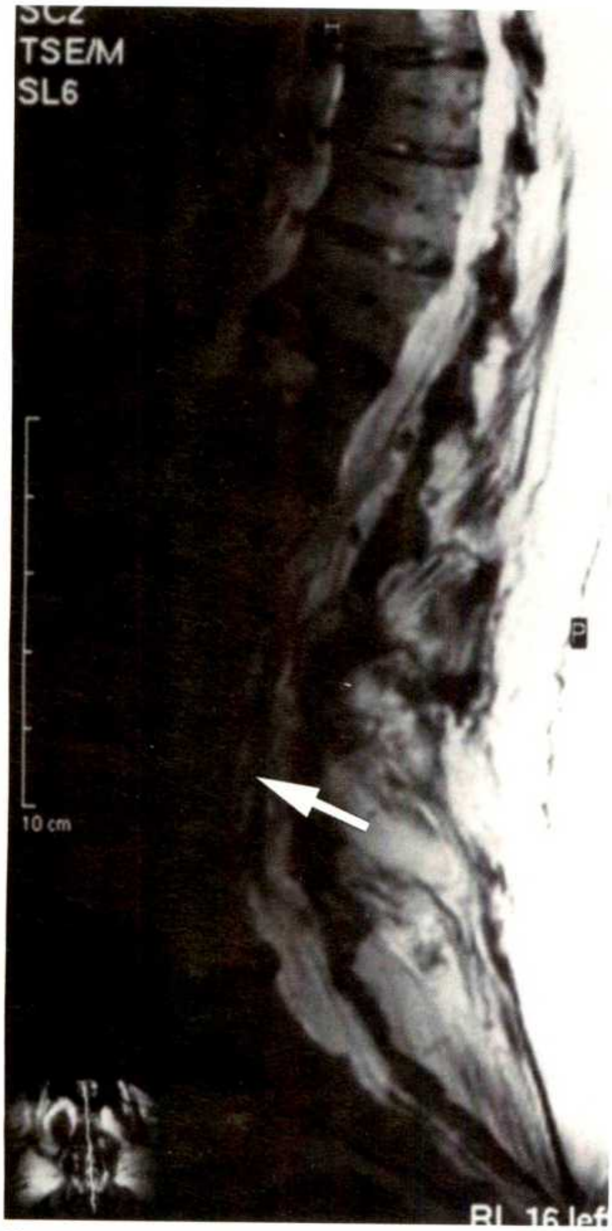

Figure 1 Sagittal view of the lumbar spine showing extradural mass extending from T11 to L5 (arrow); T2-weighted magnetic resonance image.

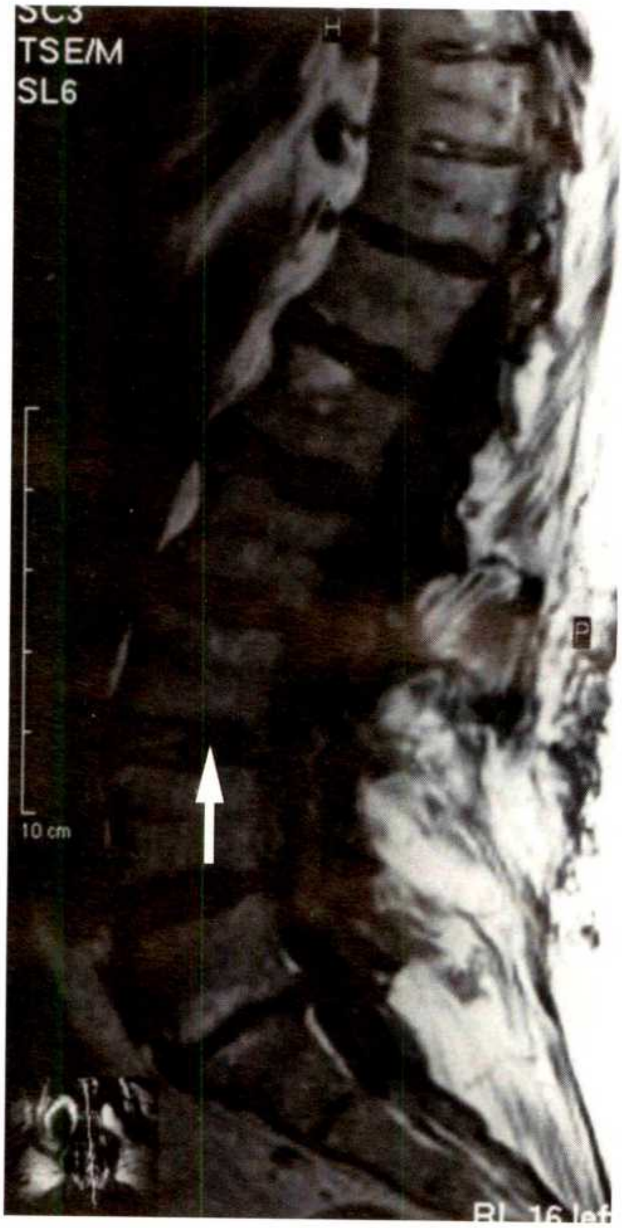

Figure 2 Sagittal view of the lumbar spine showing extradural mass extending into the L4/L5 intervertebral disc (arrow); T1-weighted magnetic resonance image.

but a sensation of positive rather than neutral or negative pressure. At this point the syringe was removed and yellow/red frothy pus passed out through the Tuohy needle.

Samples were immediately taken for urgent microbiological examination, and the extradural catheterization abandoned. Approximately 4 ml of pus drained freely before removal of the Tuohy needle. Initial bacteriological staining of the specimen showed Gram-positive cocci. *Staphylococcus aureus* was later confirmed, and had the same antibiotic sensitvities as the *Staphylococcus aureus* isolated from the blood. Mechanical ventilation was stopped successfully the next morning, on day 4 after admission. Analgesia was maintained using patient-controlled i.v. morphine. Neurological examination at this time was normal.

On day 5 the patient was referred to the local regional neurosurgical centre for magnetic resonance imaging (MRI) of her thoracolumbar spine (figs 1 and 2). This showed an extradural mass lesion extending from T11 to L5, with extension into the L4/L5 intervertebral disc. There was no evidence of spinal bony infection. The suspected diagnosis of extradural abscess was therefore confirmed. An uneventful decompressive laminectomy was performed. Patient-controlled morphine was again used for postoperative analgesia. At this stage weakness of hip flexors (L2–L3) was noted for the first time (power 3/5). A urethral catheter was passed, and high-dose i.v. flucloxacillin 2 g every 6 h was continued.

The patient made a slow recovery; at 6 weeks she was beginning to be mobile in spite of residual proximal leg weakness. No other abnormal neurology was seen on examination. A lumbar wound sinus developed, discharging yellow pus, and oral flucloxacillin was continued until this healed. When the patient was discharged home, her bladder and bowel function were entirely normal.

Discussion

Spinal extradural abscess is rare. Failure to make the correct diagnosis usually results in permanent neurological deficit for the patient. Risk factors associated with extradural abscess formation include systemic and localized infection, malignancy, immune deficiency, degenerative joint disease, diabetes mellitus and intravenous drug abuse[4]; in one review diabetes mellitus was an associated factor in 34% of extradural abscess cases described.[4] Heusner described the clincal presentation in four phases: spinal ache; root pain; weakness; and paralysis.[5] However, as demonstrated by the present case, the presentation is highly variable and may be masked by other seemingly more acute medical problems.

Of 39 patients evaluated at the Massachusetts General Hospital between 1947 and 1974, all complained of back pain, 37 were pyrexial, 35 had root pain, six complained of headache, and four noted an "electric-shock" sensation in affected limbs. In only 10 of the 39 patients was the correct diagnosis made initially, even though all had local spinal tenderness. Seven patients died and nine were left with residual neurological deficit.[3]

Early case reports describe the use of spinal/extradural needles to sound for clinically diagnosed extradural abscesses before definitive surgical decompression.[5] Myelography, for many years the diagnostic tool of choice to confirm a clinical diagnosis of extradural abscess, has been superceded by contrast-enhanced MRI. Extradural abscesses that contain no gas are difficult to diagnose on MRI without contrast enhancement, because pus gives a similar image to cerebrospinal fluid. Gadolinium-diethylenetriamine penta-acetic acid (Gd-DTPA) enhances actively inflamed tissue and so delineates the abscess cavity more clearly.[6,7] Contrast enhancement persists after clinical improvement and is thought to demonstrate granulomatous change and postsurgical scarring.

Staphylococcus aureus is consistently the most commonly isolated causative organism (62% of cases).[3,5,8,9] It is claimed that the two most important routes by which micro-organisms reach the extradural space are haematogenous spread from a distant site or direct extension from a local site, and the patient described here admitted having picked infected corns 3 weeks earlier. For this reason many anaesthetists regard systemic sepsis and local infection as contraindications to extradural analgesia.

Although there have been reports of successful conservative management of extradural abscess, surgical decompression via laminectomy is the usual treatment of choice for patients presenting with neurological deficit.[10] Surgery is normally accompanied by high-dose antibiotic therapy that includes an anti-staphylococcal agent. Two instances of successful non-surgical drainage via fluoroscopically guided Tuohy needles have been described, involving irrigation of the abscess site with saline or antibiotics.[11] In each case it was necessary to make three percutaneous needle insertions, which characteristically caused intense lower back pain upon reaching the extradural space. MRI scans performed after the procedure showed a marked decrease in the size of each abscess. Percutaneous drainage relies on the availability of high-quality imaging techniques and introduces the risk of inadvertant subarachnoid spread of infection by the drainage needles.

A review of 188 cases of spinal extradural abscess recorded between 1930 and 1982 showed that 39% of patients recovered completely, 48% had a residual neurological deficit (which in 22% was severe enough to render the patient paralysed), and 13% died.[8] Outcome is markedly affected by the interval between admission and correct diagnosis. It is adversely affected by the use of steroids, and worse if the patient has neurological deficit before surgery.[8] Overall outcome is improved if surgery is performed early, before the patient complains of weakness or paralysis.

We have described a unique presentation of extradural abscess. The coincidental diagnosis of diabetes mellitus and a pyrexia of unknown origin placed the patient in a known risk group for this condition. However, in the absence of any of the cardinal symptoms — back pain, tenderness to palpation, weakness or paralysis — the correct diagnosis was missed at presentation. After negative laparotomy the patient was admitted to the ICU. Had this patient then been denied extradural analgesia because of her history of bacteraemia, the diagnosis would almost certainly have been delayed until her neurological symptoms developed sufficiently to raise the possibility of spinal/cauda equina compression. On the other hand, had the Tuohy needle not tapped the abscess cavity, association would have been taken to imply causation, and the case would undoubtedly have been reported as an extradural abscess secondary to extradural catheterization.

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Postoperative treatment of myocardial ischaemia by thoracic extradural local anaesthetic

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Summary

This case report describes an episode of postoperative myocardial ischaemia after total oesophagectomy that was successfully treated by extradural administration of local anaesthetic. Extension of sympathetic blockade in this manner resolved the myocardial ischaemia and haemodynamic disturbances experienced by the patient. (*Br. J. Anaesth.* 1998; **80**: 848–849)

Keywords: myocardial ischaemia postoperative; analgesic techniques extradural; anaesthetics local; sympathetic nervous system block; surgery oesophageal

Thoracic extradural analgesia provides excellent postoperative analgesia after major thoracoabdominal surgery[1] and may have a positive influence on postoperative morbidity.[1-3] In patients with coronary artery disease, thoracic extradural analgesia with local anaesthetics may enable prevention and treatment of myocardial ischaemia by blocking the cardiac sympathetic nervous system.[4 5]

This case report describes the influence of thoracic extradural analgesia on postoperative ECG ischaemic episodes after oesophageal resection in a patient with coronary artery disease and chronic obstructive respiratory failure.

Case report

A 55-year-old patient (1.70 m, 74 kg, ASA III), underwent total oesophagectomy without thoracotomy, for adenocarcinoma of the lower one-third of the oesophagus.

The patient was a smoker (50 pack-years) and suffered from chronic obstructive pulmonary disease with hypoxia (Pa_{O_2} 8.5 kPa on room air) and normocapnia. FEV_1 and vital capacity were 46% and 78% of theoretical values respectively. Ultrasonic cardiography showed global hypertrophy without dysfunction of the left ventricle. Coronary arteriography revealed diffuse atheroma with stenosis (40%) of the left anterior descending and circumflex coronary arteries and right major coronary arteries. A Methergine test (0.4%) was positive with spasm of the second segment of the right coronary artery, reversible with intracoronary nitroglycerine. Systolic ejection fraction was 70%, preoperative ECG was normal and the patient had no angina. The patient was taking diltiazem and nicorandil, and inhaled β_2 sympathomimetics and corticosteroids.

After oral premedication, a thoracic extradural catheter was inserted after puncture at T7–T8. After a test dose of 3 ml and then 7 ml of lidocaine 2% with 1/200 000 adrenaline, analgesia was maintained by continuous extradural infusion (6 ml $h^{-1}$of a solution of 0.25% bupivacaine and 1 μg ml^{-1} sufentanyl. Haemodynamic monitoring consisted of a pulmonary artery catheter with continuous measurement of cardiac output (Intellicath 8F-Catheter and Vigilance Monitor, Baxter, USA) and a radial artery catheter. The perioperative ST segment was continuously monitored in leads II and V5 (Monitor M066A, Hewlett-Packard, Andover, MA, USA). Thirty min after administration of the extradural local anaesthetic, sensory block tested by the pinprick method was at T2–T12. General anaesthesia was then induced by midazolam 3 mg, propofol 150 mg, sufentanyl 25 μg and atracurium 45 mg, permitting orotracheal intubation and controlled ventilation with 60% nitrous oxide in oxygen and 0.6–1% expired isoflurane. Ventilatory parameters were stable throughout the procedure. Blood transfusion was not required. Hematocrit was 29% and body temperature was 36.5°C at the end of surgery. In addition, peri- and postoperative diltiazem i.v. 5 mg h^{-1} and nitrates 10 mg day^{-1} transdermally were administered.

Extubation was possible 1 h after operation in the post-anaesthesia care unit. Analgesia was continued by patient-controlled extradural 0.125% bupivacaine and sufentanyl 0.5 μg ml^{-1} (3 ml h^{-1} background infusion, 2.5 ml bolus, lock-out 12 min). Visual analogue scores (VAS) at rest (0=no pain, 100 mm=maximum pain) were between 10 and 25.

At 36 h, there was ST segment depression in lead 2 and elevation in V5 (ST segment shift ≥ 1 mm, at J point + 60 ms, ≥ 1 min duration), with hypertension (200/110 mmHg) and a heart rate of 85 beats min^{-1}. There was no angina or acute respiratory failure. The ECG revealed ST segment depression in the apicolateral region. Plasma potasium concentration was normal (4.1 mmol l^{-1}). The sensory block was adequate (T6-L2) with a low VAS score at rest without motor block. No analgesic bolus had been requested in the previous hour. In view of the ECG signs of myocardial ischaemia in spite of perioperative diltiazem and nitrate we gave, without effect, diltiazem bolus (20 mg) and sublingual nitrates.

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Also, a 6 ml bolus of 0.125% bupivacaine–0.5 $\mu g\ ml^{-1}$ sufentanyl solution was administered extradurally. The new sensory block extended to T1–L4 with simultanous disappearance of repolarization problems on the ST analyser and normalization of blood pressure (130/75 mmHg) and heart rate (60 beats min^{-1}). Specific myocardial enzymes were normal (5% serum creatinine kinase MB isoenzyme and concomitant myoglobin < 80 $\mu g\ l^{-1}$, troponin Ic < 0.5 $\mu g\ l^{-1}$ at 24 h).

Background infusion was increased (6 ml h^{-1}) to maintain sensory block above T4. There were no further complications.

Discussion

We describe an episode of electrocardiographic myocardial ischaemia that appeared 36 h after major thoracoabdominal surgery in a patient with coronary artery disease. This responded to blockade of the cardiac sympathetic nervous system

Mangano and colleagues showed that episodes of myocardial ischaemia are more frequent and more severe postoperatively compared with preoperatively or perioperatively in patients with high cardiac risk.[6] In addition, only 10–30% of postoperative episodes of myocardial ischaemia are linked to perioperative haemodynamic instability. These authors emphasize the protective effect of postoperative analgesia against episodes of myocardial ischaemia.[6] However, in the present case, effective analgesia did not prevent the episode. The quality of postoperative analgesia was demonstrated by low pain scores (VAS <30 mm) and presence of a sufficient sensory block (T6–L1).

This episode developed in the face of significant haemodynamic disturbances (hypertension) and resolved probably because blood pressure and heart rate were corrected. We can speculate that sympathetic nervous system block by extradural local anaesthetics induced beneficial peripheral effects (vasodilatation). On the other hand, cardiac sympathectomy by local anaesthetics could influence developement of ischaemia if it was a vasospastic phenomenon.

In a patient with coronary artery disease, cardiac sympathetic block (T1–T5) with local anaesthetics leads to a moderate reduction in cardiac output (11%), heart rate (8%) and mean arterial pressure (19%) that is easily compensated by a reduction in myocardial oxygen demand.[7 8] If the mean arterial pressure remains stable (dMAP<20%), there is no significant modification of coronary blood flow.[1] On the other hand, there is an increase in the perfusion of myocardial ischaemic territories, with favourable redistribution of coronary perfusion toward the endocardium to the detriment of the epicardium, and finally, inhibition of poststenotic coronary vasoconstriction.[1 4] De Leon-Casasola and colleagues showed that, for a quality of analgesia identical to that achieved with i.v. morphine patient-controlled analgesia after upper abdominal surgery, 5 days of patient-controlled thoracic extradural analgesia with local anaesthetics reduced the incidence of postoperative myocardial ischaemia. Among these episodes of ischaemia, 72% were silent and occurred within 36 h of surgery.[3] In cardiology, cardiac sympathetic blockade of thoracic extradural analgesia with local anaesthetics is proposed for the treatment of coronary artery disease refractory to classical treatment.[5 9 10]

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Cushing's disease treated by trans-sphenoidal selective adenomectomy in mid-pregnancy

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Summary

The clinical course and diagnosis of a patient with Cushing's disease complicated by pregnancy is described, and the anaesthetic management of trans-sphenoidal selective adenomectomy performed during the second trimester outlined. Problems included obesity, diabetes, hypertension and a suboptimal airway. Fibreoptic awake intubation and intravenous anaesthesia were used. Insulin requirements decreased substantially after surgery. Early administration of hydrocortisone after surgery avoided the risk of an addisonian crisis but delayed biochemical confirmation of a metabolic cure. (*Br. J. Anaesth.* 1998; **80**: 850–852)

Keywords: anaesthesia general; Cushing's syndrome; hypophysectomy; pituitary neoplasms; pregnancy

Cushing's syndrome is caused by excess endogenous production of corticosteroids by the adrenal glands, or their exogenous administration. Most cases of endogenous hypercortisolaemia are caused by an adrenocorticotrophin (ACTH) secreting pituitary microadenoma and the condition is then known as Cushing's disease. Of the remaining cases most are caused by a unilateral adrenal adenoma, rarer causes being an ACTH-secreting carcinoid tumour, adrenal carcinoma, micro- or macronodular adrenal hyperplasia, and aberrant expression of peptide hormone receptors within the adrenal cortex. In contrast, adrenal adenomas are the most common cause of Cushing's syndrome when it occurs in pregnancy.[1]

Cushing's syndrome is rarely associated with pregnancy because of disturbances of menstruation and the associated infertility caused by the hypercortisolaemia. When pregnancy does occur maternal morbidity and mortality are increased as a result of hypertension, diabetes, pre-eclampsia, cardiac failure and poor wound healing after Caesarean section. For the fetus there is an increased risk of spontaneous abortion, stillbirth, premature labour, intrauterine growth retardation and perinatal death. Of 69 cases reviewed by Sheeler,[1] only 27 were attributable to pituitary disease, and 87% developed maternal or fetal complications. In a review of the management of Cushing's syndrome during pregnancy Buescher[2] described 17 patients who had received treatment directed at correcting the hypercortisolaemia, including unilateral or bilateral adrenalectomy, one case of trans-sphenoidal surgery,[3] pituitary irradiation, and drug therapy with metyrapone and cyproheptadine. Within this small group there were no stillbirths in contrast to five in a group of 43 women who had received supportive therapy only. The perinatal death rate, however, remained high in the treated group (2/17 *vs* 8/43 : treated *vs* untreated), and little different from that in cases where no attempt was made to treat the hypercortisolaemia. The major maternal adverse outcomes — death and congestive heart failure — were seen only in women who had received supportive treatment alone.

There have been three previous reports of Cushing's disease treated successfully during pregnancy by trans-sphenoidal surgery.[3-5] In this small number of uncontrolled cases the outcome of pregnancy was favourable for both mother and fetus. As the approach offers a relatively simple, non-pharmacological opportunity to correct the metabolic disturbance before the onset of perinatal maternal complications, it has been suggested that, provided confident diagnosis of a pituitary aetiology has been made, trans-sphenoidal surgery is the management of choice.[5 6]

We report a patient who underwent trans-sphenoidal resection of an ACTH-secreting pituitary microadenoma while pregnant.

Case Report

A morbidly obese 40-yr-old female (height 1.45 m, weight 120 kg, body mass index 57 kg m^{-2}) presented with a recent history of weight gain and the development of diabetes mellitus, which was managed initially with diet and oral hypoglycaemic drugs. Subsequent investigation revealed a raised urinary free cortisol concentration of 928 nmol 24 h^{-1} (normal value <340 nmol 24 h^{-1}) and a blood pressure of 210/130 mm Hg. Physical examination revealed the typical physical features of Cushing's syndrome. The diagnosis was confirmed by a loss of the normal diurnal serum cortisol rhythm (sequential midnight sleeping cortisol levels 641 nmol l^{-1} and 336 nmol l^{-1}), and a failure of the 09:00 serum cortisol to suppress below 50 nmol l^{-1} after oral dexamethasone 0.5 mg q.d.s. for 48 h (09:00 cortisol 152 nmol l^{-1}). A probable pituitary aetiology was suggested by the finding of further suppression of serum cortisol to 46 nmol l^{-1} after high-dose dexamethasone

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(2 mg q.d.s. for 48 h), a plasma ACTH concentration within the normal range at 45 ng l^{-1}, and bilateral adrenal hypertrophy on a computed tomography scan. However sampling in the basal state from the inferior petrosal sinuses, which drain the pituitary, failed to demonstrate any gradient in plasma ACTH concentration between the sinuses and simultaneously sampled peripheral blood. (Post-stimulation samples were not possible as human corticotrophin releasing hormone (CRH) was temporarily unavailable in the UK at the time of investigation).

At this stage of her investigations the patient became pregnant and was started on insulin therapy. Control of the diabetes was difficult with initial HbA1c fractions of up to 10.3% (reference value <6.2%). Up to 148 units of insulin per day were required to achieve near normoglycaemia.

During further investigation with a peripheral CRH test there was a significant rise in serum cortisol concentration from a baseline of 427 nmol l^{-1} to a maximum of 983 nmol l^{-1} at 1 h, suggesting a pituitary aetiology for the Cushing's syndrome rather than an ectopic ACTH source, where the response is typically flat. Magnetic resonance imaging was unsuccessful at the first attempt because of claustrophobia, but subsequent imaging after sedation with oral temazepam showed a pituitary microadenoma, central and superior in the gland.

After careful discussion of the potential risks and potential benefits of surgery the patient agreed to an elective, mid-trimester trans-sphenoidal selective adenomectomy.

Her medical history was otherwise unremarkable, and included uncomplicated anaesthesia for tonsillectomy and a long history of obesity predating the onset of Cushing's syndrome.

At the preoperative visit she was noted to have a short but mobile neck and a mobile larynx. Mouth opening was good but only the upper half of the uvula was visible. All the anterior teeth on the upper jaw were crowned. She found the supine position very uncomfortable and could not tolerate it for more than a minute. She was also claustrophobic and unable to tolerate a face mask. She was premedicated with glycopyrronium 0.6 mg i.m. and oral ranitidine 300 mg.

After establishing venous access and standard monitoring, and giving supplementary oxygen, she was lightly sedated with midazolam without loss of verbal contact (total dose 4 mg over 15 min). Following application of topical lidocaine an awake fibreoptic orotracheal intubation was performed. Anaesthesia was induced and maintained with propofol and alfentanil infusions and intermittent doses of atracurium. After induction of anaesthesia, arterial blood pressure was measured directly via a radial artery cannula. Fetal heart beat was confirmed before and after surgery using a Doppler device. Fetal movements were felt shortly after wakening and recurred with normal frequency thereafter.

After induction of anaesthesia, systolic blood pressure was initially stable (115–135 mm Hg), but then rose to 160 mm Hg in spite of bolus doses of propofol and alfentanil. Subsequently, 50% nitrous oxide was added and haemodynamic stability was restored. A total of 1950 mg of propofol and 22 mg of alfentanil were given over 155 min (average rates of administration 6.3 mg kg^{-1} h^{-1} and 71 µg kg^{-1} hr^{-1} respectively). At the end of surgery, which lasted 140 min, neuromuscular block was antagonized and the patient extubated wide awake in a semi-upright position.

Perioperatively, the patient's diabetes was managed with dextrose and insulin infusions begun on the evening before surgery and adjusted according to blood glucose estimations. Blood glucose concentration remained normal during surgery. Postoperatively, insulin requirement decreased dramatically from 150 units per day to 40 units in the 24 h after surgery. On the second and third days after operation, her insulin requirement fell to 30 and 20 units respectively. It is our usual practice to delay giving steroid replacement for 24 h after surgery for Cushing's disease, to permit the measurement of serum cortisol as an early index of metabolic cure (cortisol <50 nmol l^{-1}). However in this case the risks of delaying the first dose were deemed unacceptable and steroids were given i.v. at 6 h.

Histological examination of the operative specimen showed fragments of an ACTH-secreting pituitary tumour.

The patient was discharged from the neurosurgical unit to a hospital nearer her home 5 days after surgery, having made an uneventful recovery. Treatment on discharge comprised oral hydrocortisone 30 mg in divided doses, which was withdrawn for a brief period to facilitate a short synacthen test. This demonstrated a normal serum cortisol response to tetracosactrin, allowing for the pregnancy-induced elevation in cortisol-binding globulin, (0 min 467 nmol l^{-1}, 30 min 982 nmol l^{-1}) indicating early recovery of the hypothalamic–pituitary-adrenal axis. Serum thyroxine levels remained normal and there was a normal thyrotrophin (TSH) response to thyrotrophin-releasing hormone (TRH).

Hydrocortisone and insulin in reduced doses were continued for the remainder of the pregnancy, which was complicated by severe pre-eclamsia. The patient was delivered of a live male infant at 34 weeks gestation by an emergency Caesarean section under general anaesthesia, because of concern over impending eclampsia. The infant had a birth weight of 2300 g and APGAR scores of 7, 8 and 10 at 1, 5 and 10 min respectively. The child was admitted routinely to the special care baby unit, and was bottle fed, although normal lactation was established in the mother. Since the delivery, after which hydrocortisone therapy was discontinued, the patient's urinary free cortisol excretion has been within the normal range and her insulin requirements have continued to decline.

Discussion

The diagnosis of Cushing's disease in the patient described here was complicated by the difficulty in obtaining magnetic resonance images, the misleading petrosal sinus ACTH results, the initial unavailability of human CRH, and the effect of the oestrogen-induced elevation in cortisol-binding globulin on the interpretation of total serum cortisol levels. Interpretation of magnetic resonance images of the pituitary during pregnancy is also complicated by changes related to normal pregnancy.[7]

The decision to operate on this patient was justified by the high incidence of maternal and fetal obstetric complications in the absence of intervention in Cushing's syndrome,[1] and the additional problem of steroid-induced diabetes with marked insulin resistance. The benefits of intervention for Cushing's syndrome during pregnancy remain uncertain,[2] and must be weighed against the potential risks of anaesthesia, the operative procedure and any drug therapy used. Given the rarity of the problem it is unlikely that randomized controlled trials will be performed, and existing publications are relatively unhelpful. Anecdotally, wound complications after caesarean section are less likely if the hypercortisolaemia is corrected antenatally by definitive surgery.[6] Drug therapy with metyrapone, an inhibitor of 11 β-hydroxylase, has been used with some success,[9] but is theoretically unattractive. The drug can cross the placenta and hence inhibit fetal cortisol synthesis,[10] while although maternal cortisol also crosses the placenta, little enters the fetal circulation because of the high activity of placental 11 β-hydroxysteroid dehydrogenase and its consequent conversion to biologically inactive cortisone.[11]

The middle trimester of pregnancy is generally regarded as a suitable period for essential elective surgery during pregnancy,[12] and there is no evidence that any well conducted anaesthetic technique is superior to any other.[12]

We selected awake fibreoptic intubation of the trachea because of the combined risk factors of pregnancy, a suboptimal airway and morbid obesity. Use of a limited amount of sedation facilitated this procedure in an exceptionally anxious patient. Our anaesthetic technique was selected to give satisfactory conditions for neurosurgery with rapid recovery. The addition of nitrous oxide after 1 h was a pragmatic decision; the alternatives would have been additional narcotic or antihypertensive medication. Our anaesthetic technique worked well and we were able to achieve tracheal extubation without coughing with the patient wide awake and semi-upright, this being the only position in which she could breathe comfortably.

We considered using continuous fetal monitoring during and after surgery but the patient's extreme obesity made it likely that this would have been at best intermittent. We also felt that frequent interruptions in the fetal signal would seriously alarm both the patient and attending staff in a situation where there were few therapeutic options. Accordingly we used intermittent fetal monitoring before and after surgery with no fetal monitoring during surgery.

The high insulin requirement of this patient confirmed the experience of others.[1] The sharp fall in insulin requirement after surgery reflects the reduction in adrenal cortisol output and was suggestive of a successful procedure, although definitive confirmation of remission was not possible until after a trial of hydrocortisone withdrawal in the postpartum period. Although it would have been desirable to confirm a biochemical cure by withholding steroid treatment and finding a low serum cortisol immediately after operation, we considered the risks of hypotension or addisonian crisis to be unacceptable in mid-pregnancy. Accordingly steroid replacement was started early.

In summary the differential diagnosis and management of Cushing's syndrome during pregnancy poses a great challenge for both physician and obstetrician. In this case elective trans-sphenoidal selective adenomectomy during pregnancy produced an apparent metabolic cure without immediate anaesthetic or surgical complications. Although the outcome was favourable in that there was no long-term maternal morbidity, and a healthy live infant was delivered, the perinatal problems were nevertheless substantial and potentially life threatening for both mother and fetus as a result of the severe pre-eclampsia.

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Death associated with disseminated intravascular coagulation after hip replacement

S. W. LOGAN

Summary

Sudden-onset disseminated intravascular coagulation (DIC) occurred 3 h after uneventful polymethacrylate bone cement insertion for a revision left Charnley hip replacement. Profuse bleeding caused a hypovolaemic state aggravating existing myocardial ischaemia; as a result death occurred secondary to myocardial infarction 6 h after operation. (*Br. J. Anaesth.* 1998; **80**: 853–855)

Keywords: complications disseminated intravascular coagulation; complications myocardial ischaemia; surgery orthopaedic bone cement insertion

Immediate cardiopulmonary effects are the most common adverse reactions to methylmethacrylate (MMA) bone cement insertion.[1-5] In the absence of hypovolaemia, hypotension is regarded as uncommon (incidence less than 5%) in elective hip surgery.[6] Hypoxia and hypotension are more common in patients who are elderly, have pre-existing hypertension, uraemia or are having emergency surgery for transcervical femoral fractures.[1 7] The aetiology of these reactions is thought to be pulmonary microembolism of fat and thromboplastic products.[3 5]

A previously unreported manifestation of cement insertion, the delayed onset of sudden catastrophic haemostatic failure, is presented.

Case report

An 88-year-old woman was admitted electively for revision hip surgery. She had previously had two cemented prostheses inserted; loosening of the cemented prosthesis on the left had necessitated a revision.

On preoperative assessment she was noted to have a history of rheumatic fever, a cerebrovascular accident and a partial gastrectomy for drug-induced ulceration. She was receiving aspirin 75 mg. The patient weighed 35 kg with a body mass index of 15. She was in atrial fibrillation with a heart rate of 120 beats min^{-1} and blood pressure was 120/70 mm Hg. An ECG revealed left ventricular hypertrophy on voltage criteria (37 mm) and ischaemia in the lateral leads (V_5 and V_6). Echocardiography demonstrated moderate left ventricular function, and the chest radiograph showed mild cardiomegaly (cardiothoracic ratio 0.65). Her haemoglobin was 12.1 g dl^{-1} and platelet count 194×10^9 l^{-1}.

The patient was started on digoxin, receiving digoxin 0.75 mg orally the night before surgery. A final dose of 0.25 mg was omitted, as the heart rate was 65 min^{-1} at 08:00 on the morning of surgery. No premedication was given. At induction of anaesthesia the blood pressure was 116/70 mm Hg and heart rate 100 beats min^{-1}. After instigation of non-invasive monitoring and preoxygenation, anaesthesia was induced. An epidural catheter was sited at L1–L2 and a central venous pressure line inserted. Anaesthesia was maintained during intermittent positive pressure ventilation with nitrous oxide 66%, oxygen 33%, isoflurane 0.4–1.2%.

The intraoperative course was unremarkable, apart from a rise in blood pressure to 200/100 mm Hg during the initial skin incision, with S-T segment depression on the electrocardiogram; the blood pressure and ischaemic changes were quickly controlled using an i.v. infusion of glyceryl trinitrate. There was no significant change in blood pressure, heart rate, arterial oxygen saturation (Sp_{O_2}), or end-tidal carbon dioxide (FE'_{CO_2}) with reaming or cement insertion into the acetabulum or femur. Central venous pressure was 7–10 mm Hg throughout the procedure. Blood loss during the 155-min procedure was estimated to be less than 500 ml. Intraoperative fluids were 2 l of Hartmann's solution and 500 ml Haemaccel. A unit of blood was started immediately the operation was finished.

After an uneventful 90 min in the recovery room, the patient was transferred to an intensive care area for monitoring and management of extradural analgesia. On arrival there it was noted that her axillary temperature was 32.5°C and 400 ml of blood had drained from the wound drain since skin closure. A Bair Hugger warming blanket was applied and an epidural infusion started using fentanyl 15 μg h^{-1} and bupivicaine 7.5 mg h^{-1}. Soon after transfer to the intensive care area, the patient's blood pressure decreased to 64/32 mm Hg. This responded to a further unit of blood and 500 ml of Haemaccel, which increased the central venous pressure from 3 to10 mm Hg, and discontinuing the glyceryl trinitrate infusion. However 25 min later the blood pressure was 85/60 mm Hg with associated S-T segment depression on the ECG. There was no evidence of a low intravascular volume, with central venous pressure 8 mm Hg, heart rate 80 beats min^{-1} and no

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new loss into the wound drains. The extradural infusion was stopped and metaraminol 1 mg in increments of 0.5 mg given i.v. This produced an immediate rise in blood pressure to 120/70 mm Hg.

Sudden reduction in systolic blood pressure to 40 mm Hg occurred 15 min later, and 1800 ml of unclotted, partially haemolysed blood was noted in the previously empty drains. A provisional diagnosis of disseminated intravascular coagulation (DIC) was made and a coagulation screen and fresh frozen plasma and platelets requested. In spite of vigorous fluid resuscitation with three units of blood and increments of epinephrine to a total of 0.5 mg, an asystolic cardiac arrest occurred. After a bolus of atropine 3 mg and a bolus of epinephrine 2 mg, a rhythm of atrial fibrillation with intermittent idioventricular rhythm was established. Arterial blood gases showed pH 7.473, Pa_{CO_2} 3.42 kPa, Pa_{O_2} 10.2 kPa, base deficit –3.2 mmol l^{-1}, and haematocrit 26%. An epinephrine infusion was started (15μg min^{-1}) and 1.5 l of hydroxyethyl starch 6% (Hespan) given to keep the central venous pressure at 8–10 mm Hg. Thirty min after the cardiac arrest the blood pressure was 110/60 mm Hg, central venous pressure 12 mm Hg and heart rate 120 beats min^{-1} (atrial fibrillation with a left bundle branch block), but there was oozing from venepuncture sites, haematuria and no clot in the wound drains. Clotting screen from the time of cardiac arrest showed a platelet count of $< 10 \times 10^9$ l^{-1}, haemoglobin 9.9 g dl^{-1}, prothrombin time (PT) seven times normal and thrombin time 40 s (control 14 s). Activated partial thromboplastin time (APTT) had no end point. Six units of platelets and four units of fresh frozen plasma were given.

Over the next 60 min, in spite of an epinephrine infusion (50 μg min^{-1}), the patient had repeated asystolic cardiac arrests. She was hypoxic and acidotic on 100% oxygen; arterial blood gases showed pH 7.08, Pa_{O_2} 5.3 kPa, Pa_{CO_2} 6.40 kPa, and base deficit –13.4 mmol l^{-1}. Repeat coagulation screen showed continuing consumption of clotting factors, with a haemoglobin of 5.5 g dl^{-1}, platelets 17×10^9 l^{-1}, APTT >240 s, and PT 9.8 times normal. Three more units of blood were given while awaiting delivery of further clotting factors. Asystole progressed to electromechanical dissociation, and 215 min after the patient was admitted to intensive care it was decided to discontinue resuscitation as further attempts were unlikely to be beneficial.

The postmortem examination showed death to have been caused by myocardial infarction; the anterior two-thirds and posterior third of the left ventricle showed recent evidence of infarction, without demonstrable occlusive coronary atheroma. There was no significant aortic valve disease, but mitral valve thickening and incompetence consistent with rheumatic fever were noted

Discussion

The cause of death was an extensive myocardial infarction. Although myocardial ischaemia was associated with the hypertension associated with skin incision, this was quickly controlled with glyceryl trinitrate. After operation, there were the additional stresses of hypothermia (axilla temperature 32.5°C), anaemia and hypovolaemia. Hypovolaemic shock precipitated by a sudden onset coagulopathy was the main factor responsible for the myocardial infarction which resulted in her death.

The possible causes of disseminated intravascular coagulation in this patient are fat emboli from the bone cement and prosthesis insertion, delayed hypersensitivity reaction to bone cement, a transfusion of incompatible blood, and sepsis. In addition, the haemodilutional effects of the administration of 4.5 l of fluid, the effects on coagulation of administration of 1.5 l of Hespan and moderate hypothermia, need to be considered.

The contribution of direct microvascular occlusion by fat emboli to the myocardial ischaemia is unknown, as evidence for this was not specifically sought during the postmortem examination. Fat globules were, however, detected in the plasma and urine, indicating that fat embolism had taken place, although no petechiae were noted. None of the organ samples obtained at autopsy were stained for the presence of fat. Haematological derangement of this magnitude has not been previously noted in studies of fat embolism after lower limb fractures[8] or hip surgery.[9]

There have been conflicting reports of the magnitude and significance of histamine release in response to cement insertion.[10] [11] However Monteny[12] felt that a severe hypersensitivity reaction to methylmethacrylate cement was unlikely to cause severe coagulopathy. Enquiry to the manufacturers of acrylic cement (Palcos R with gentamicin, Schering-Plough, Mildenhall, Suffolk) revealed no experience of this complication.

The blood bags of the transfused units were returned to the laboratory, and testing revealed no evidence of bacterial infection or incompatibility. The transfusion therefore appeared unlikely to be the cause of the haemolysis and DIC. There was no evidence of sepsis from the preoperative urine, nasal swabs or postmortem examination.

Of the other possible contributing factors, hypothermia is known to cause a thrombocytopenia proportional to its degree.[13] At 32°C a 30–50% reduction in platelet count could be expected because of sequestration in the liver and gut. Before the coagulopathy became evident the patient had received 2 l of Hartmann's solution and 1 l of Haemaccel, resulting in significant dilution (estimated blood volume being 2450 ml): the haematocrit at this point was 0.26. Haemaccel has not been associated with any interference with coagulation.[14] However, after the onset of the coagulopathy, 1.5 l of Hespan was administered before blood became available. As well as diluting clotting factors, this has been observed to decrease the concentration of factor VIII and von Willibrand's factor,[15] prompting the recommendation to limit administration to 20 ml kg^{-1} day^{-1}. Recent studies have not found any prolongation of clotting times or reduction in platelet count after using 1 l of Hespan in cardiac surgery,[16] neurosurgery or gynaecology.[17] However, Boldt and colleagues[14] found a decrease in platelet aggregation associated with an increase in blood loss when they gave Hespan to cardiac surgery patients.

Profound coagulation failure occurred in the initial postoperative period. There was evidence of fat in the urine and sputum at postmortem examination. The combination of fat emboli, haemodilution, hypothermia and possibly the effect of Hespan administration is most likely to have triggered the coagulopathy that resulted in haemorrhagic shock and myocardial infarction. The relative importance of each factor could not be ascertained. More rapid access to coagulation factors, which have to be requested and then sent by road from the regional transfusion centre, may have allowed the coagulopathy to be controlled earlier before major blood loss and myocardial ischaemia occurred.

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Holt–Oram syndrome

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Summary

Holt–Oram syndrome (HOS) is a rare disorder characterized by congenital anomalies of the upper limbs and heart. Cardiac arrhythmias are common in patients with HOS. We successfully managed a 24-yr-old woman with HOS who underwent laparoscopic ovarian cystectomy. Potential problems in the anaesthetic management of patients with HOS are discussed. (*Br. J. Anaesth.* 1998; **80**: 856–857)

Keywords: anaesthetic techniques extradural; complications arrhythmia; complications Holt–Oram syndrome

Holt–Oram syndrome (HOS) is a rare disorder characterized by congenital anomalies of the upper limbs and heart.[1–4] Cardiac arrhythmias, irrespective of the presence or absence and severity of cardiac anomalies, often accompany HOS.[1–3] Moreover, sudden death can occur in these patients.[4]

We managed a woman with HOS who underwent laparoscopic ovarian cystectomy after extradural anaesthesia supplemented with light general anaesthesia. There were no untoward events. Potential problems in the anaesthetic management of patients with HOS are discussed.

Case report

A 24-yr-old Japanese woman was to undergo laparoscopic ovarian cystectomy. Her parents, two brothers, and close relatives had no abnormalities of the upper limbs or heart.

She underwent a cardiac catheterization when 5 yr old after the detection of heart murmurs. Cannulation of the femoral veins was difficult but successful after several attempts. Ventricular septal defect and aortic regurgitation became apparent. The association of anomalies of the heart with those of the upper extremities (short right humerus, agenesis of thumbs, and hypoplastic index fingers) led to a diagnosis of HOS. Patch closure of the ventricular septal defect and aortic valvoplasty were performed when she was 9 yr old. A brief episode of supraventricular tachycardia occurred immediately after that operation, and electrocardiogram (ECG) revealed a transient Wolff–Parkinson–White (WPW) syndrome.

Atypical genital bleeding occurred 2 months before the present operation. An ultrasonogram of the lower abdomen revealed a left ovarian cyst of about 8 cm diameter. Laparoscopic ovarian cystectomy was arranged. There had been no documented episodes of tachycardia other than that following closure of her ventricular septal defect.

Physical examination before operation revealed anomalies of the upper extremities — hypoplastic clavicles and pectoralis major muscles and abducens palsy — and ocular refractive error. Chest x-ray showed a cardiothoracic ratio of 0.54, without increase in pulmonary vascular markings. Routine ECG showed strain-type ST–T changes in leads V4–V6. There were no delta waves. Continuous ambulatory Holter monitoring recorded five supraventricular and 20 monofocal ventricular premature contractions each day; however, there were no conduction abnormalities or tachycardia.

The patient was premedicated 2 h before surgery with pentobarbital 100 mg and diazepam 10 mg orally and 30 min before surgery with atropine 0.4 mg s.c. On arrival in the operating theatre arterial pressure was 142/76 mm Hg and heart rate 88 beat min^{-1}. ECG monitoring was established, together with monitoring of arterial pressure (noninvasive) and central venous pressure, pulse oximetry and capnography. An extradural catheter was inserted in the Th12/L1 intervertebral space. Two percent mepivacaine 3 ml was given via the catheter. There was no discernible hypoaesthesia in the lower limbs after 2 min. The central venous pressure was 9 cm H_2O. Injection of 2% mepivacaine 7 ml produced an area of hypoaesthesia to cold from Th6 to S3 after 5 min. The arterial pressure, heart rate and central venous pressure were 148/70 mm Hg, 82 beat min^{-1}, and 8 cm H_2O, respectively.

Anaesthesia was induced with thiopental 150 mg i.v. supplemented with butorphanol 1 mg and midazolam 3 mg. The trachea was intubated after vecuronium 4 mg i.v. Anaesthesia was maintained with nitrous oxide (67%) in oxygen, and ventilation was mechanically controlled. Laparoscopic ovarian cystectomy was begun after intraperitoneal insufflation of carbon dioxide with a pressure of 8 mm Hg. There were no haemodynamic changes of note during the surgery, which lasted 2 h 25 min. The trachea was extubated after neostigmine 2.5 mg and atropine 1.0 mg i.v. There was no conduction disturbance or supraventricular tachycardia during or after anaesthesia and surgery. The patient was discharged well 6 days after surgery.

Discussion

Holt–Oram syndrome is either familial or, in 30-85% of patients,[2] occurs in isolated cases. Familial HOS is

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transmitted as an autosomal dominant trait and related, in most subjects, to mutations in a gene on chromosome 12q.[5] The severity of upper-limb anomalies and anomalies of the heart shows a positive correlation that increases with successive generations.[4] Subjects in HOS families with anomalies of the upper limbs but no heart anomalies are diagnosed as having HOS, because they can transmit both anomalies to their offspring, but the presence of both anomalies is a prerequisite for the diagnosis of HOS in isolated cases. Subjects with isolated HOS tend to have more severe anomalies of the upper limbs than do familial cases.[4] As our patient's family and close relatives had no anomalies of the upper limbs or heart, she was apparently an isolated case.

Hypoplastic thumbs are suggestive of HOS. Of 98 subjects with hypoplastic thumbs, 16 (16%) proved to be cases of HOS.[6] The anomalies of the upper limb in HOS vary in severity. They range from only hypoplasia of the thumb, clinodactyly, brachydactyly, syndactyly or hypoplasia to agenesis of the radius or humerus or both, and ectromelia. Other associated anomalies often observed are hypoplasia of the clavicle and pectoralis major,[1–4,7] and, less frequently, abducens palsy and ocular refractive error.[4] As preoperative examination for non-cardiac surgery in adults with HOS sometimes discloses cardiac anomalies,[4] it is important precisely to evaluate the cardiovascular system before any surgery in patients with hypoplastic thumbs.

We have found no reports on the management of patients with HOS in the English anaesthetic literature from 1966 to 1997. Potential problems in the management of such patients are associated with their cardiac anomalies, cardiac arrhythmias, and the hypoplastic vasculature.

Atrial and ventricular septal defects are common cardiac anomalies in individuals with HOS. Of 189 patients with HOS having cardiac anomalies, the most frequent single anomaly was atrial septal defect (41.8%), followed by ventricular septal defect (13.8%).[3] Both of these defects are often associated with other heart anomalies. More complicated anomalies, such as tetralogy of Fallot, endocardial cushion defect and total anomalous pulmonary venous return, were observed in 33 (17.5%) of 189 subjects with HOS.[3] In those who have moderate to severe cardiac anomalies, heart surgery is performed between the postnatal period and early childhood. The survival of individuals with HOS depends on the severity of their cardiac anomalies. Of the 189 subjects with HOS and heart anomalies, 12 (6.3%) died (the causes of death were not stated); all had moderate or severe heart anomalies. They constituted 36% of the 33 patients in this series with moderate or severe cardiac anomalies.[3]

Various types of arrhythmia occur in subjects with HOS.[1–4,8] Most subjects with HOS who had arrhythmias had anatomical heart anomalies.[2,4] However, 39% of those with familial HOS showed only ECG abnormalities and no anatomical heart anomalies.[4] Spontaneous closure of atrial and ventricular septal defects with ageing cannot be ruled out in such subjects. Arrhythmias observed in subjects with HOS include sinus arrest, sinus node dysfunction, wandering pacemaker, bradycardia, atrial fibrillation, atrioventricular block and right bundle branch block.[1,2,4,8,9] Some patients needed a permanent cardiac pacemaker.[2] Sudden death occurred in some HOS patients with no documented cardiac anomalies.[4] Our patient had had transient supraventricular tachycardia and a transient WPW syndrome after operation for patch closure of the ventricular septal defect when 9 yr old. We found no reports of WPW syndrome in subjects with HOS.

Hypoplastic vasculatures are present in subjects with HOS. There are reports of patients in whom cardiac catheterization through femoral or arm veins was difficult.[1,9] When our patient underwent cardiac catheterization when 5 yr old, to evaluate the anomalies of the heart, multiple femoral vein punctures were required. Some individuals with HOS have hypoplastic clavicles and pectoralis majors,[2,9] and radial arteries that are difficult to palpate.[10] It may be more reliable and safer in patients with HOS to cannulate blood vessels under ultrasound guidance,[11] because their anatomical landmarks are different from those of normal subjects.

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CITATION CLASSIC

Commentary

Nunn JF, Bergman NA, Coleman AJ. Factors influencing the arterial oxygen tension during anaesthesia with artificial ventilation. *British Journal of Anaesthesia* 1965; **37**: 898–914.

This paper demonstrates how what we know about pulmonary gas exchange has developed through the years since the Second World War. Not only did Dr Nunn apply recent advances in the oxygen electrode to demonstrate impaired oxygenation, he also used the developing theoretical concepts of gas exchange to interpret the impairment that was found. He cites the fundamental work of Farhi and Rahn, who unravelled the knot of ventilation–perfusion relationships, using a graphical method to match gas tensions in blood and alveolar gas. Farhi went on to develop the early computer models of gas exchange, which ultimately led to the multiple inert gas infusion technique for assessing the distribution of ventilation–perfusion ratios. (As an aside, thegases, which include halothane or one of the other volatile anaesthetics, are far from truly inert.) This work with computer models was pioneered by Kelman, who developed computer routines to convert oxygen tension into haemoglobin saturation, publishing his paper in the same year as this one, 1965.

Nunn cites the paper of his co-author Bergman, who found that lung volume was reduced in the anaesthetized subject. Bergman had already studied gas distribution in anaesthesia, but it was not until the more powerful radioisotope methods pioneered in the Royal Postgraduate Medical School, Hammersmith, were applied by Milic-Emili to demonstrate airway closure, that some of the direct mechanisms for impaired gas exchange began to emerge.[1] The demonstration of airway closure was able to explain the phenomenon of lung collapse observed by Nunn in the lungs of volunteers after breathing oxygen, while the lung volume was voluntarily reduced. This paper, published in the same year, is also cited. Later work from the Hammersmith was to show how the simple gravity-dependent model was not the whole story,[2] as we are discovering in patients who require intensive care. The densities, and the associated hypoxaemia, could be reversed by restoring lung expansion. We know from the studies of Hedenstierna, using computed tomography (CT) images of the lung, that patches of increased radiological density appear in the lungs of patients during anaesthesia.[3] These are lesser examples of the phenomenon that Nunn had himself generated, and Hedenstierna has shown that the changes on CT are more marked with oxygen breathing.[4]

Dr Nunn used the then recent concept of "ideal alveolar gas" and the three-compartment model of gas exchange, both developed by Riley.[5] Nunn recognized the difficulty of comparing gas-transfer efficiency by means of oxygen tension alone, ifthere should be at the same time a change in the alveolar oxygen tension; the values will be "at different points on the oxygen dissociation curve". He therefore assumes a constant arteriovenous oxygen content difference to allow the impairment to be quantified "as if" it were shunt. Although the arteriovenous difference may not remain constant, particularly during surgery such as was studied here, it is greatly preferable to the common method used nowadays of the Pa_{O_2}/FI_{O_2} ratio, which ignores this more complex relationship, and seems to have been embraced by intensivists merely because it is easy to calculate.

Nunn applied the concept that, by using 100% oxygen, the influence of lung regions with small ventilation/perfusion ratios can be eliminated. He found that the impairment of gas exchange persisted, and concluded that the impairment was therefore mainly caused by shunting in the collapsed lung, although there remained "the possibility that marked inequality of ventilation/perfusion does exist under the conditions of the study". What he did not consider was the phenomenon of pulmonary vascular reactivity. Hypoxia constricts pulmonary vessels, and this allows some control of the matching of perfusion to ventilation. Anaesthetics inhibit this reflex. Sykes,[6] who also worked at the Royal Postgraduate Medical School, was one of those who studied the effects of anaesthetics on these responses. Consequently, the effects of small regions of collapse, partly resulting from the high oxygen concentration, may have been amplified by the effects of anaesthetic agent on vascular tone.

Nowadays, our appreciation of the range of factors that can affect pulmonary vascular behaviour, such as nitric oxide, endothelin, prostanoids,[7] and other inflammatory mediators, and the factors that can affect distribution of ventilation such as PEEP and posture, make us understand how complex a field the apparently simple topic of "alveolar–arterial difference" has become.

Nunn was applying recently developed ideas, in particular those of the ideal alveolar gas, but these had not yet yielded the entire range of concepts and methods that we have now to assess gas exchange.

The most important has been the inert-gas technique, although this method may be unnecessarily complex. Intrinsic gases may be just as useful, and certainly more practical.[8]

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FACTORS INFLUENCING THE ARTERIAL OXYGEN TENSION DURING ANAESTHESIA WITH ARTIFICIAL VENTILATION

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SUMMARY

Factors influencing oxygenation of the arterial blood were studied in 26 patients, during routine anaesthesia with artificial ventilation. The mean minute volume was 10 l./min and the arterial P_{CO_2} 27 mm Hg. The mean oxygen consumption was 215 ml/min (STPD) and the physiological deadspace 36 per cent of tidal volume (no allowance being made for the volume of the air passages bypassed by the endotracheal tube). At high levels of inspired oxygen concentration, the mean alveolar-arterial P_{O_2} gradient was 145 mm Hg, corresponding to a calculated shunt of 11 per cent. At an alveolar P_{O_2} of 155 mm Hg the gradient was 52 mm Hg, corresponding to a calculated venous admixture of 9 per cent. There was no progressive increase in venous admixture during anaesthesia in patients under the age of 43 but most of the older patients showed falls and their mean change was significant. Attempts were made to reduce the venous admixture by hyperinflation of the lungs. This was successful in some patients, when a pressure of 40 cm H_2O was maintained for 40 seconds. Lower pressures, and the use of a sustained expiratory pressure of 5 cm H_2O were not effective. Indices of disordered respiratory function found in this study were not significantly different from those in a comparable study of anaesthetized patients breathing spontaneously.

A previous publication described the factors which influence arterial oxygen tension during anaesthesia with spontaneous respiration (Nunn, 1964). The present study is an extension of that work designed to evaluate the same factors during anaesthesia with artificial ventilation. In other respects, the circumstances and the analytical techniques of the two studies have remained the same but it has proved possible to increase the number of measurements made on each patient. We have, therefore, been able to observe changes in the factors influencing arterial oxygen tension during the course of anaesthesia. This has been of particular interest since the study of Bendixen, Hedley-Whyte and Laver (1963), reporting progressive falls in arterial oxygen tension during anaesthesia.

METHODS

Patients and anaesthesia.

A total of 60 sets of measurements were carried out in 26 patients (8 male) (table I). Most of the patients had neither clinical nor radiological evidence of cardiac or respiratory diseases, the exceptions being noted in table I. The consent of each patient was sought and they

	Primary symbols		*Secondary symbols*
V	gas volume	A	alveolar
$\dot{V}$	gas flow rate or exchange	I	inspired
F	fractional concentration	E	expired
P	tension	D	deadspace
R	respiratory exchange ratio	T	tidal
f	respiratory frequency	a	arterial

STPD standard temperature and pressure dry

BTPS body temperature and pressure saturated

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TABLE I

Details of patients studied.

Patient	Age	Sex	Height (cm)	Weight (kg)	Surface area (sq.m)	Premedication	Operation	Position	Rectal Temperature (°C)	Medical state
Group I										
C.M.	69	F	157	66	1.65	B	Vaginal hysterectomy	Lithotomy	36.4	Fit
S.S.	50	F	167	74	1.83	E	Hysterectomy	Supine	36.4	Aortic stenosis
M.B.	45	F	162	62	1.64	D	Hysterectomy	Supine	36.5	Fit
E.S.	56	F	160	66	1.69	B	Repair of urethro-vaginal fistula	Lithotomy	36.1	Fit
A.C.	70	M	178	67	1.82	B	Right soleal denervation	Prone	36.3	Hypertension
P.G.	23	M	163	81	2.02	D	Varicose veins	Supine	36.0	Fit
J.K.	37	M	178	67	1.82	D	Vagotomy	Supine	35.8	Fit
E.H.	41	F	167	55	1.60	A	Total hysterectomy	Supine	36.0	Fit
J.B.	59	M	170	68	1.78	B	Herniorrhaphy	Supine	36.6	Fit
R.S.	42	M	180	74	1.92	A	Endarterectomy	Supine	35.4	Fit
E.P.	66	F	165	57	1.61	None	Excision of cyst and total hysterectomy	Supine	37.5	Fit
E.B.	64	F	157	77	1.77	None	Oophorectomy	Supine	36.0	Fit
E.S.	54	F	162	59	1.62	B	Radium to cervix	Lithotomy	36.0	Chest metastases
A.R.	55	F	167	57	1.63	B	Total hysterectomy	Supine	35.9	Fit
M.R.	59	F	160	70	1.72	B	Vaginal repair	Lithotomy	36.4	Fit
E.M.	64	F	157	64	1.63	A	Vaginal repair	Lithotomy	36.1	Hypertension
J.S.	32	F	167	62	1.69	None	Total hysterectomy and salpingectomy	Supine	36.1	Fit
B.B.	40	F	162	62	1.65	None	Peritoneoscopy	Supine	36.1	Fit
Group II										
R.F.	54	F	152	59	1.55	B	Radium to cervix	Lithotomy	36.3	Fit
A.T.	67	F	155	57	1.55	B	Radium to cervix	Lithotomy	35.8	Hypertension
J.H.	27	F	167	65	1.65	C	Tuboplasty	Supine	35.8	Fit
T.C.	52	M	172	78	1.90	A	Iliac endarterectomy	Supine	35.3	Healed P.T.
G.W.	55	F	162	60	1.63	A	Hysterectomy	Lithotomy	36.6	Fit
W.T.	64	M	175	73	1.87	B	Gastrectomy	Supine	36.6	Fit
P.P.	34	F	170	56	1.64	B	Excision melanoma of thigh	Supine	36.6	Fit
A.G.	58	M	175	57	1.69	A	Closure vesico-colic fistula	Supine	36.0	Fit
Mean	51		166	65	1.71				36.2	

Premedication: A=papaveretum 20 mg, atropine 0.6 mg

B=pethidine 100 mg, atropine 0.6 mg

C=papaveretum 20 mg, hyoscine 0.4 mg

D=morphine 16 mg, atropine 0.6 mg

E=pethidine 50 mg, atropine 0.6 mg, promethazine 50 mg remained under the care of anaesthetists who were not concerned with making measurements in the study: premedication varied according to their custom (table I). Arterial puncture was carried out prior to induction in those patients who we considered would not be distressed by this procedure, and the mean value of arterial Po_2 was 85 mm Hg in 8 patients of mean age 49 years: mean Pco_2 was 39 mm Hg.

Anaesthesia was induced with thiopentone (200–500 mg). Patients were then intubated with cuffed endotracheal tubes, during paralysis produced with suxamethonium (50–100 mg), and muscular relaxation was maintained using either tubocurarine or gallamine. In the patients belonging to group I, anaesthesia was maintained with a nitrous oxide and oxygen mixture, supplemented by intravenous pethidine when required. The concentrations of oxygen are shown in table II. Anaesthesia for the patients in group II was maintained by a halothane and oxygen mixture without nitrous oxide. This permitted the attainment of the high concentrations of inhaled oxygen shown in table II.

In all patients the lungs were ventilated artificially with a Manley ventilator. This was driven by a gas pump which drew the inspired gas mixture from a reservoir linked to a spirometer (fig. 1). For the greater part of the anaesthetic, the exhaled gas was vented to atmosphere. During the periods of measurement, however, the fresh gas supply was interrupted and the exhaled gas was diverted into the bag suspended within the fresh gas reservoir. This operated as a box-bag system and permitted the measurement of the difference between the inspired and expired minute volume (Nunn and Pouliot, 1962). However, due to the varying amount of gas retained

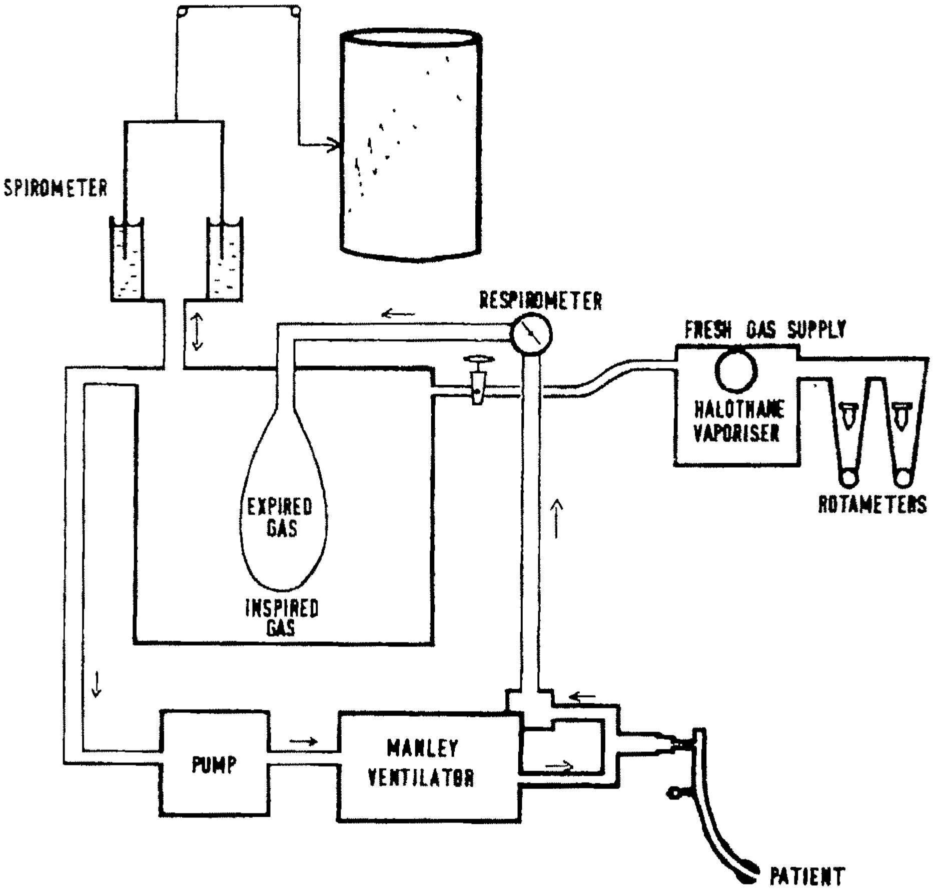

FIG. 1

Gas circuit used in the study. In between measurement periods, expired gas was allowed to vent to atmosphere. During measurement periods, it was collected in the bag. The respirometer was calibrated against the spirometer using the patient's expiratory flow pattern.

within the Manley ventilator during the different phases of the respiratory cycle, the spirometer trace did not indicate the tidal exchange of the patient. Ventilation was therefore measured with a Wright respirometer mounted in the expiratory pathway. The repeatability of this instrument is extremely high, although its calibration is influenced by minute volume, composition of respired gas and the respiratory waveform. We calibrated it, therefore, against a spirometer, for each patient, under the conditions prevailing during the measurement periods. Apart from these modifications, which were required by the use of artificial ventilation, the arrangements for gas collection and sampling were the same as those employed for the study during spontaneous respiration (Nunn, 1964).

Gas analysis.

Carbon dioxide concentrations were measured with a carbon dioxide - sensitive electrode (Severinghaus and Bradley, 1958). It was established that the output of the electrode bore a linear relationship to the log of the carbon dioxide concentration down to 1 per cent. which was lower than any concentration encountered in the present study. The limitations due to the accuracy of this technique are discussed at length by Nunn and Pouliot (1962). Oxygen concentrations were measured with a Servomex DCL 101 paramagnetic analyzer. The discrimination, replicability and probably the absolute accuracy are comparable with that obtained with the Haldane apparatus. It is, furthermore, far more convenient and may be used in the presence of nitrous oxide (Nunn et al., 1964).

Blood analysis.

The collection, handling and analysis of arterial blood samples followed the procedure described by Nunn (1964). P_{CO_2} was measured with a carbon dioxide-sensitive electrode (Severinghaus and Bradley, 1958) with a random error whose coefficient of variation was 4 per cent. P_{O_2} was determined polarographically using the system described by Bishop and Pincock (1958). The random error was somewhat less than that reported in previous studies with a coefficient of variation of 3.5 per cent. Corrections were applied for the time interval between sampling and analysis, dilution of samples by heparin and for any temperature difference between patients and the electrodes (Nunn et al., 1965).

Calculation of results.

Ideal alveolar P_{O_2} was derived from the following form of the Filley equation:

$$P_{A_{O_2}} = P_{I_{O_2}} - Pa_{CO_2}\left(\frac{P_{I_{O_2}} - P_{E_{O_2}}}{P_{E_{CO_2}}}\right) \text{ (Nunn, 1963)}$$

and the venous admixture derived from a mixing equation using the assumptions listed by Nunn (1964). We have made considerable use of the calculated venous admixture in reporting our results since it is difficult to compare the significance of changes in alveolar and arterial P_{O_2} when studies are made at different points on the oxygen dissociation curve.

Calculations of venous admixture are open to the criticism that the mixed venous oxygen content is assumed rather than measured, and we did not consider it justifiable to sample blood from the right ventricle under the conditions of this study. Recent observations (Theye and Tuohy, 1965; Sykes, Young and Robinson, 1965) have suggested that it might well be more reasonable to assume an arteriovenous oxygen content difference of 5 volumes per cent. rather than 3.5 volumes per cent which we have used in this study and in the previous study during spontaneous respiration (Nunn, 1964). In any case, the calculation of venous admixture lacks precision since two components (from Thebesian and bronchial veins) have an oxygen content which is probably quite different from that of mixed venous blood. The reader is at liberty to make his own estimate of the likely oxygen content of the blood comprising the venous admixture under the conditions of this study. If he thinks that 5 volumes per cent is a more likely figure for arteriovenous oxygen content difference then the values for venous admixture reported in this study and that of Nunn (1964) should be reduced by about 25 per cent.

The physiological deadspace was derived from Bohr's equation using arterial P_{CO_2} and correcting for apparatus deadspace (50 ml).

Oxygen consumption was determined by the method of Nunn and Pouliot (1962), and is expressed as a percentage of basal according to the calorific data of Aub and Dubois (1917) and Boothby and Sandiford (1924). Their values are now considered rather high, being about 15 per cent above results obtained in well-rested subjects (Robertson and Reid, 1952).

Measures taken to re-expand atelectatic lung.

Following control measurements of venous admixture, three methods were tried to re-expand the lung:

(1) Threshold resistance was introduced into the expiratory gas circuit by dipping the open end of the expiratory tubing 5 cm below the surface of the water. This was maintained for 8 minutes during which arterial blood samples were taken at the end of the 1st, 2nd, 4th and 8th minutes. A final sample was withdrawn after removal of the resistance.

(2) The lungs were held inflated at a pressure of 30 cm H_2O for 30 seconds. Arterial blood samples were then withdrawn after the 1st, 2nd, 4th and 8th minutes.

(3) The lungs were held inflated at a pressure of 40 cm H_2O for 40 seconds, samples being withdrawn as described above.

RESULTS

The mean minute volume was 10.3 l./min (BTPS), of which approximately 750 ml/min represented ventilation of apparatus deadspace. This ventilation resulted in a *mean arterial* Pco_2 of 26.6 (range 17.5–41.6) mm Hg (table II). Values for Pco_2 tended to decline during the first 50 minutes of anaesthesia but thereafter there was no systematic change.

The mean physiological deadspace / tidal volume ratio was 36 per cent. and tended to increase with the age of the patient (fig. 2). The correlation coefficient was +0.57 and highly significant (0.001<P<0.01). In nine patients, it was possible to make three or more measurements of the VD/VT ratio. Mean values for the first, second and third observations showed no evidence of an increase in VD/VT ratio with duration of anaesthesia (table III).

The mean oxygen uptake of the patients in Group I was 215 ml/min (STPD). The mean dioxide output was 180 ml/min (STPD) and the

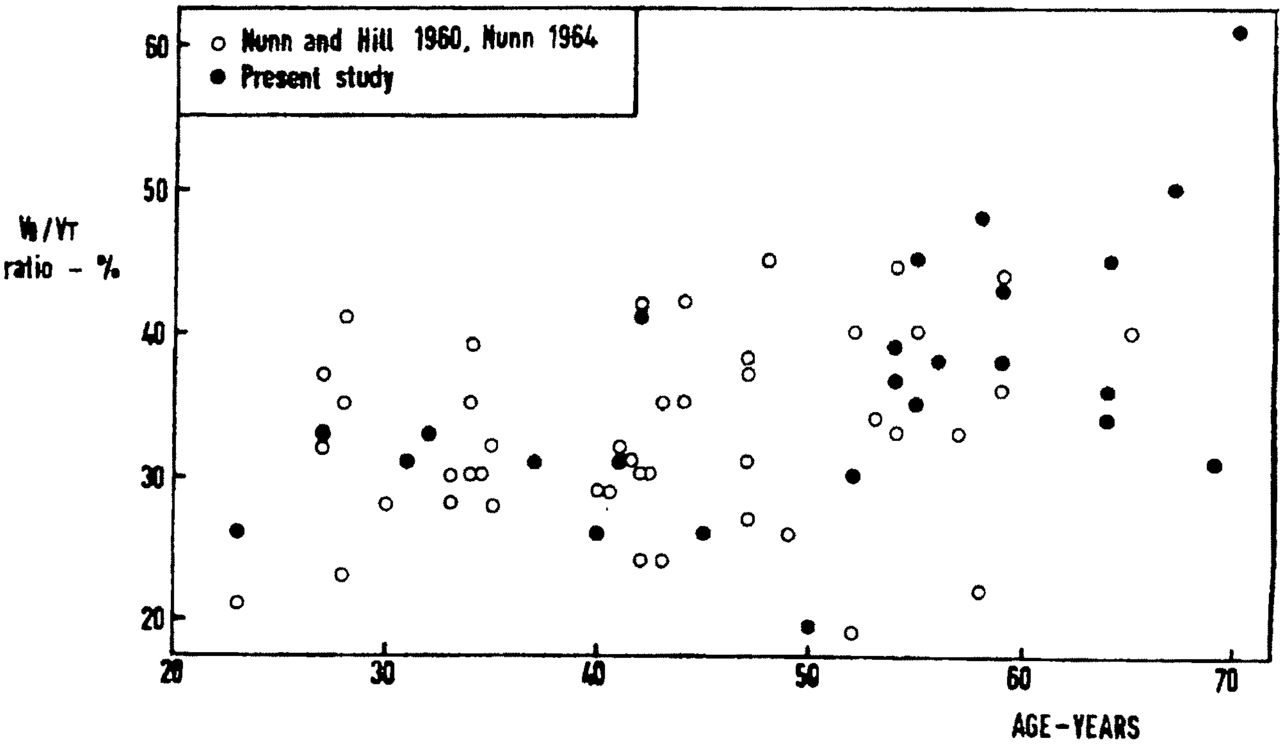

Fig. 2

Physiological deadspace/tidal volume ratio plotted against the age of the patients. For the present study there is a positive correlation (r = +0.57) which is highly significant. The correlation coefficient for the previous studies are +0.37 and +0.34, neither of which is significant.

respiratory exchange ratio was 0.84 (table II). There is no evidence of any systematic change of oxygen uptake during anaesthesia, but the respiratory exchange ratio and carbon dioxide output tended to fall during the first hour of anaesthesia. After 1 hour the mean respiratory exchange ratio was 0.75.

Inert gas exchange averaged 250 ml/min at 20 minutes, 150 ml/min at 40 minutes and 120 ml/min at 60 minutes after induction (tables II and VII). These figures, together with the difference between oxygen uptake and the carbon dioxide output, account for the difference between the inspired and the expired minute volume.

The arterial Po_2 had a mean value of 102 (range 63–166) mm Hg in the patients of Group I who had a mean inspired oxygen concentration of 25.17 per cent (table II). The lowest arterial Po_2 was 63 mm Hg in a patient (E.M.) who was breathing 27.70 per cent oxygen. This patient had hypertension but no evidence of respiratory disease. In group II, the mean inspired oxygen concentration was 98.06 per cent and the mean arterial Po_2 was 517 (range 421–636) mm Hg.

Alveolar-arterial Po_2 difference had a mean value of 52 (range 12–125) mm Hg in the patients of Group I who had a mean alveolar Po_2 of 155 mm Hg (table II). In Group II, the mean alveolar-arterial Po_2 difference was 145 (range 40–234) mm Hg at a mean alveolar Po_2 of 662 mm Hg.

Calculated venous admixture had a mean value of 9.3 per cent in Group I and 10.8 per cent in Group II, the two values not being significantly different. When plotted against duration of anaesthesia (fig. 3), the calculated venous admixture in the patients under the age of 42 years showed no significant change during anaesthesia

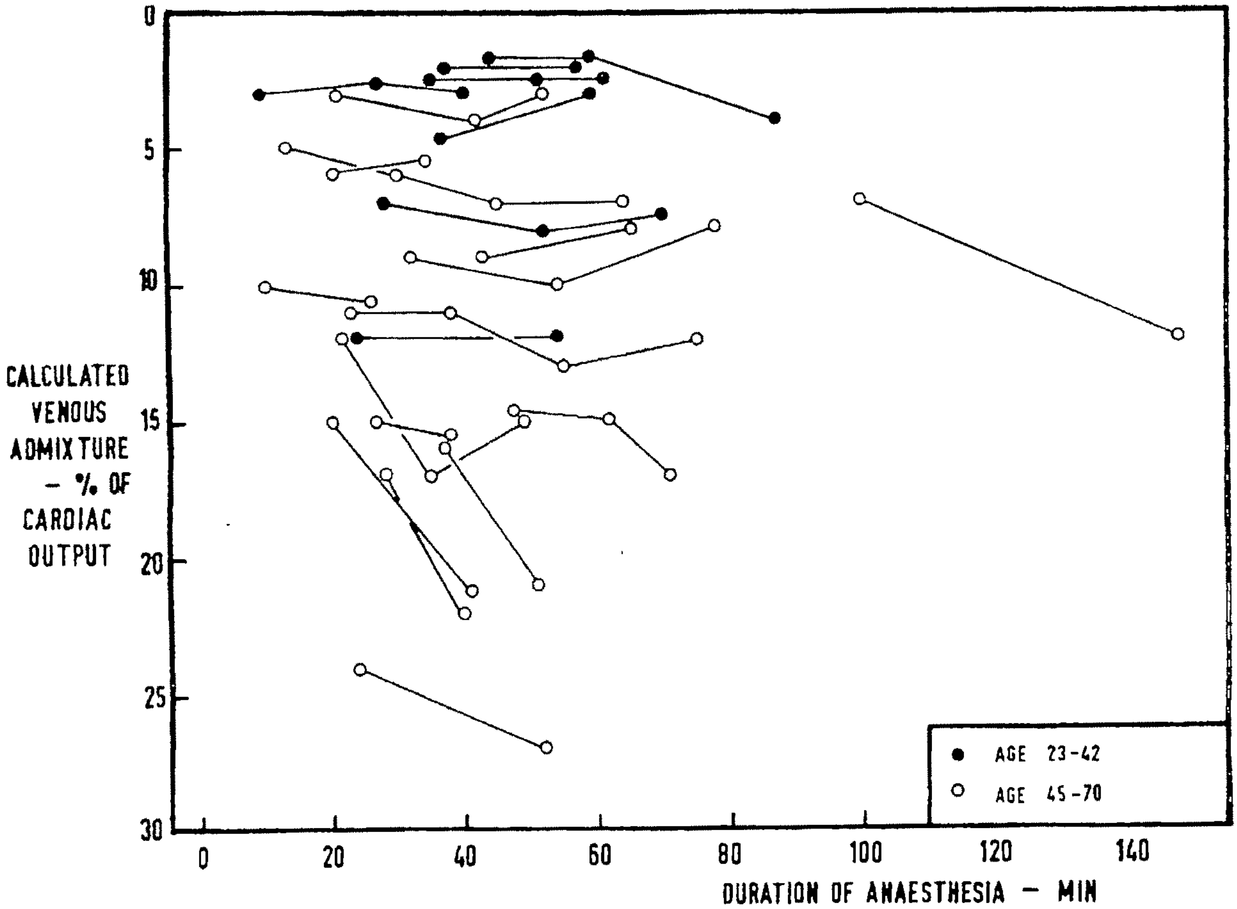

FIG. 3

Calculated venous admixture plotted against the duration of anaesthesia shows no significant change in the patients aged between 23 and 42. Patients aged between 45 and 70 show an increase of calculated venous admixture (mean value 0.11 per cent/min) which is significant.

TABLE II

Observed and derived data.

Patient	Time from induction (min)	FI_{O_2} (%)	$\dot{V}_I$ (l./m BTPS)	f (BPM)	$\dot{V}_E$ (ml/ BTPS)	Pa_{CO_2} (mm Hg)	PA_{O_2} (mm Hg)	Pa_{O_2} (mm Hg)	A-a P_{O_2} difference (mm Hg)	Calculated venous admixture (%)	V_D/V_T ratio (%)	$\dot{V}_{O_2}$ (ml/min STPD)	$\dot{V}_{O_2}$ (% of basal)	R	Inert gas uptake (ml/min STPD)
Group I															
C.M.	13	23.35	10.49	14.0	730	23.4	145	113	32	5	32.0	187	97	0.89	192
	30	23.30	10.33	14.1	717	21.5	145	106	39	6	27.0	191	100	0.87	157
	45	22.25	10.33	13.9	725	21.0	138	95	43	7	31.0	185	97	0.80	163
	65	22.04	10.47	14.0	731	20.7	132	98	34	7	34.0	202	105	0.70	137
S.S.	21	24.50	10.90	14.7	723	20.9	153	86	67	12	22.0	223	100	0.82	184
	35	24.00	10.99	14.6	735	19.4	153	74	79	17	16.9	207	93	0.89	195
	49	23.80	10.86	14.4	740	19.4	149	79	70	15	23.6	204	91	0.81	124
M.B.	28	22.75	11.54	15.1	745	20.2	140	72	68	17	32.0	216	106	0.75	186
	40	22.60	10.65	14.4	720	18.3	147	64	83	22	27.0	198	98	0.73	172
E.S.	23	23.35	10.40	13.9	720	27.6	142	84	58	11	39.0	219	108	0.79	276
	38	23.20	10.37	13.5	747	27.9	141	84	57	11	39.9	195	96	0.89	233
	55	23.33	10.20	13.3	750	25.9	139	81	58	13	42.4	193	95	0.80	185
	75	23.04	10.04	13.3	741	24.9	135	81	46	12	41.0	190	93	0.78	115
A.C.	20	23.53	10.06	14.0	697	39.7	131	98	33	6	69.0	208	92	0.83	214
	33	23.70	10.54	14.6	699	41.6	128	94	34	6	53.0	241	106	0.81	221
P.G.	9	21.30	10.05	13.8	689	34.6	126	114	12	3	31.1	269	98	0.88	450
	27	21.70	10.21	13.6	723	30.0	131	111	20	3	19.0	278	101	0.91	289
	40	21.49	10.29	13.7	730	30.5	124	107	17	3	27.0	270	99	0.87	247
J.K.	28	22.70	11.25	13.8	785	26.2	146	103	43	7	29.0	201	81	1.04	361
	52	22.90	10.51	13.7	741	25.3	139	96	43	8	30.0	253	102	0.73	233
	70	22.72	9.82	13.4	714	25.2	136	96	40	8	33.0	230	93	0.73	149
E.H.	35	24.80	9.47	12.4	755	27.5	155	129	26	3	28.0	190	95	1.03	103
	51	24.60	9.04	12.2	728	25.5	154	135	19	3	33.0	176	88	0.90	122
	61	24.68	9.07	12.2	729	26.5	151	138	13	3	32.0	208	104	0.62	75
J.B.	21	22.89	10.44	14.7	679	36.0	138	115	23	3	38.0	270	117	0.84	353
	42	22.98	9.01	13.0	670	34.0	138	110	28	4	39.0	209	90	0.88	224
	52	23.07	8.80	12.8	669	34.1	134	112	22	3	37.0	228	98	0.83	150
R.S.	44	25.95	9.48	13.0	715	30.5	155	138	17	2	40.0	220	86	0.81	127
	59	27.20	9.16	13.0	695	28.0	165	145	20	2	43.0	187	73	0.80	66
	88	25.50	9.18	13.0	700	28.5	153	126	27	4	41.0	192	75	0.83	33
E.P.	20	26.60	9.49	13.1	697	29.6	171	86	85	15	31.0	217	115	0.89	276
	40	25.90	9.67	13.5	696	30.0	163	72	91	21	31.0	209	111	0.97	218
E.B.	37	31.10	10.22	12.9	771	29.0	203	86	117	16	32.0	214	103	0.93	221
	51	31.70	10.22	12.8	784	26.5	198	73	125	21	37.0	242	117	0.71	86

E.S.	15	29.65	9.62	13.3	697	27.5	187	104	83	10	42.0	225	115	0.66	219
	26	29.45	9.36	13.1	700	26.2	193	102	84	11	34.0	161	82	1.01	162
A.R.	52	28.05	10.41	13.6	748	26.7	177	136	41	5	45.0	198	100	0.77	158
M.R.	43	27.60	11.24	14.4	766	29.3	179	112	67	9	39.0	195	93	1.04	90
	65	27.80	10.90	14.3	748	27.3	174	110	64	8	46.0	200	96	0.80	134
E.M.	24	27.75	11.23	14.5	765	27.1	177	70	107	24	38.0	173	89	1.13	144
	52	27.70	10.93	14.4	753	23.3	177	63	114	27	35.7	184	91	0.94	62
I.S.	23	29.40	10.98	15.9	675	29.4	190	104	86	11	38.3	228	107	0.86	168
	54	27.28	11.79	16.0	709	23.4	174	97	77	11	27.9	278	131	0.71	287
B.B.	37	29.95	11.03	13.4	801	33.4	187	166	21	2	36.2	281	135	0.80	190
	57	29.80	11.62	14.6	780	30.0	187	162	25	3	36.9	266	128	0.86	151
Mean		25.17	10.28			27.4	155	102	52	9.3	35.1	215	99	0.84	
Standard deviation							21.7	24.7	30.8	6.5					
Standard error of the mean							3.2	3.7	4.5	0.97					
Group II															
R.F.	27	98.90	9.01	13.6	663	26.9	666	455	211	15	36.7				
	38	98.80	9.55	13.7	696	23.9	675	461	214	15	—				
A.T.	12	99.25	9.93	15.2	656	20.0	671	530	141	11	49.8				
J.H.	36	98.90	12.74	15.7	811	22.8	673	629	44	4	36.0				
	59	98.90	11.76	16.0	735	20.3	676	636	40	3	29.5				
T.C.	49	95.70	10.09	15.5	652	28.4	642	504	138	11	40.2				
G.W.	32	98.62	9.10	16.2	560	21.2	664	546	118	9	38.7				
	54	97.97	10.26	16.5	623	19.1	669	534	135	10	33.0				
	78	97.89	10.27	16.2	640	19.8	669	568	101	8	35.6				
W.T.	37	98.40	9.60	16.4	586	29.6	647	444	203	15	—				
	62	98.40	10.10	16.2	623	31.4	648	437	211	15	—				
	71	98.44	10.00	16.2	619	29.5	655	421	234	17	45.4				
P.P.	60	98.57	12.60	21.4	587	17.5	679	535	144	11	26.0				
A.G.	100	94.40	11.50	17.1	669	25.8	636	554	82	7	49.2				
	120	97.90	10.50	18.1	574	28.4	663	507	156	12	47.2				
Mean		98.06	10.46			24.3	662	517	145	10.8	38.9				
Standard deviation							13.4	65.7	61.8	4.1					
Standard error of the mean							3.4	16.9	15.9	1.1					

(the mean increase was 0.011 per cent shunt/minute which did not approach the customary level of significance). However, in patients between 45 and 70 years of age, the mean increase in calculated venous admixture was 0.11 per cent shunt/minute and this was significant ($0.01<P<0.02$). When the calculated venous admixture (interpolated value at 30 minutes) was plotted against age (fig. 4), a tendency was seen for the venous admixture to increase with the age of the patient. The correlation coefficient was +0.38, the value for P being very close to 0.05.

Effect of hyperinflation on calculated venous admixture. There was no significant change in calculated venous admixture when a threshold resistor of 5 cm H_2O was applied to the expiratory gas circuit (fig. 5). The actual values for arterial Po_2 also showed no change. A sustained inflation of 40 cm H_2O for 40 seconds caused a reduction in calculated venous admixture in four patients, with no change in a fifth patient who had a control value of only 5 per cent and could not therefore be expected to show much improvement (fig. 6). A sixth patient showed a small increase in calculated venous admixture during the first 2 minutes after hyperinflation: unfortunately, the arterial cannula blocked after 2 minutes and further measurements could not be made on this patient. The decrease in calculated venous admixture was mirrored by changes in arterial Po_2 but the changes in the small number of patients studied did not reach the customary level of statistical significance. When the lungs were inflated at 30 cm H_2O for 30 seconds (fig. 6) there were no systematic changes in arterial Po_2 or in calculated venous admixture.

Hyperinflation caused severe cardiovascular disturbances. Intra-arterial blood pressure was not measured but the pulse disappeared entirely from the wrist and it was not possible to measure the blood pressure by the Riva-Rocci method. The pulse returned immediately the hyperinflation was discontinued and the blood pressure rapidly regained its control value.

DISCUSSION

The previous study of factors influencing arterial Po_2 during anaesthesia with spontaneous respiration (Nunn, 1964) listed four factors tending to lower the arterial Po_2. The first of these was underventilation, which was eliminated in the present study since almost every patient

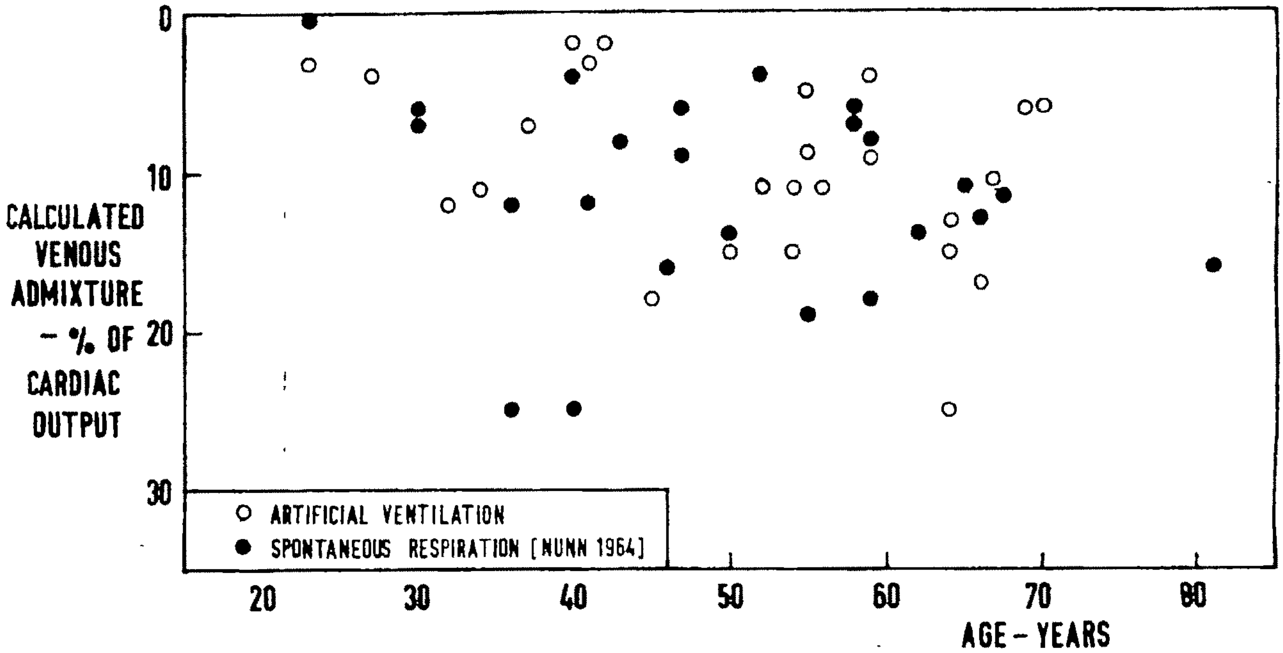

FIG. 4

Calculated venous admixture plotted against age shows an increase which closely approaches significance at the 95 per cent confidence limit ($r=+0.38$) for results reported in the present study but not those of the previous study during spontaneous respiration (Nunn, 1964).

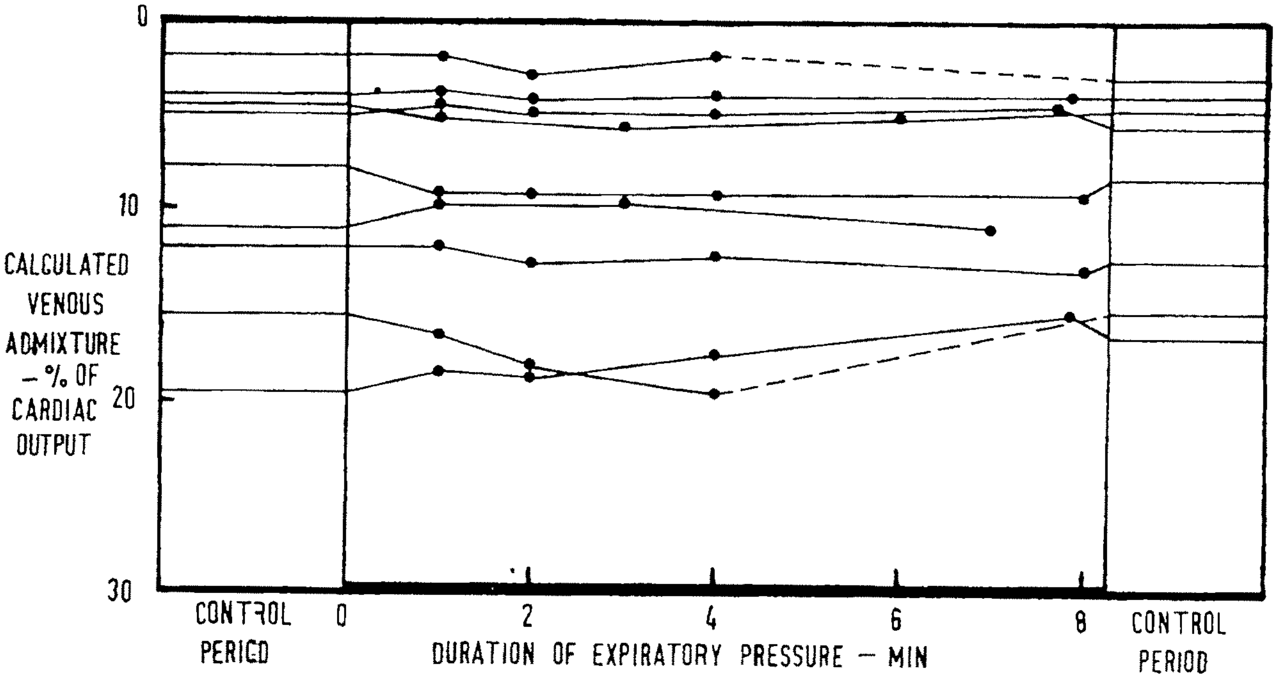

FIG. 5
Calculated venous admixture did not diminish when the expiratory pressure was raised to 5 cm H_2O.

showed evidence of alveolar hyperventilation with hypocapnia.

The second factor was increased physiological deadspace which is known to be a regular feature of general anaesthesia. Values for VD/VT ratio in the present study are not significantly different from those observed in previous studies during anaesthesia with spontaneous respiration (Nunn and Hill, 1960; Nunn, 1964), and also during artificial ventilation (Campbell, Nunn and Peckett, 1958; Nunn and Hill, 1960). The increase of VD/VT ratio with age (fig. 2) is probably due in part to the prevalence of some degree of chronic respiratory disease in older patients. We have been unable to confirm the progressive increase in physiological deadspace which was suggested by Thornton (1960) and unequivocally demonstrated by Askrog et al. (1964) during artificial ventilation with a variety of anaesthetic agents. Their results spanned 150 minutes, which was probably sufficiently long to show changes which were not revealed in the much shorter time covered by our own observations (table III).

TABLE III
Effect of duration of anaesthesia on physiological deadspace (9 patients).

Mean duration of anaesthesia (min)	Mean VD/VT ratio (%)
25	32
42	31
59	32

The third and most important factor tending to reduce the arterial Po_2 is admixture of shunted venous blood with oxygenated blood leaving the pulmonary capillaries. It is currently thought that this is largely due to circulation through atelectatic lung. Table IV compares the calculated shunts observed under similar conditions with spontaneous and artificial ventilation, at high and moderate levels of arterial Po_2. Two trends may be noted in our own studies of anaesthetized patients. Firstly, the venous admixture is slightly larger during spontaneous respiration at both levels of alveolar Po_2. Secondly, the venous admixture is slightly greater at the higher levels of alveolar Po_2 during both types of ventilation. The differences are not significant at the customary levels of confidence but this does not exclude the possibility that the depressed ventilation associated with spontaneous respiration may be more

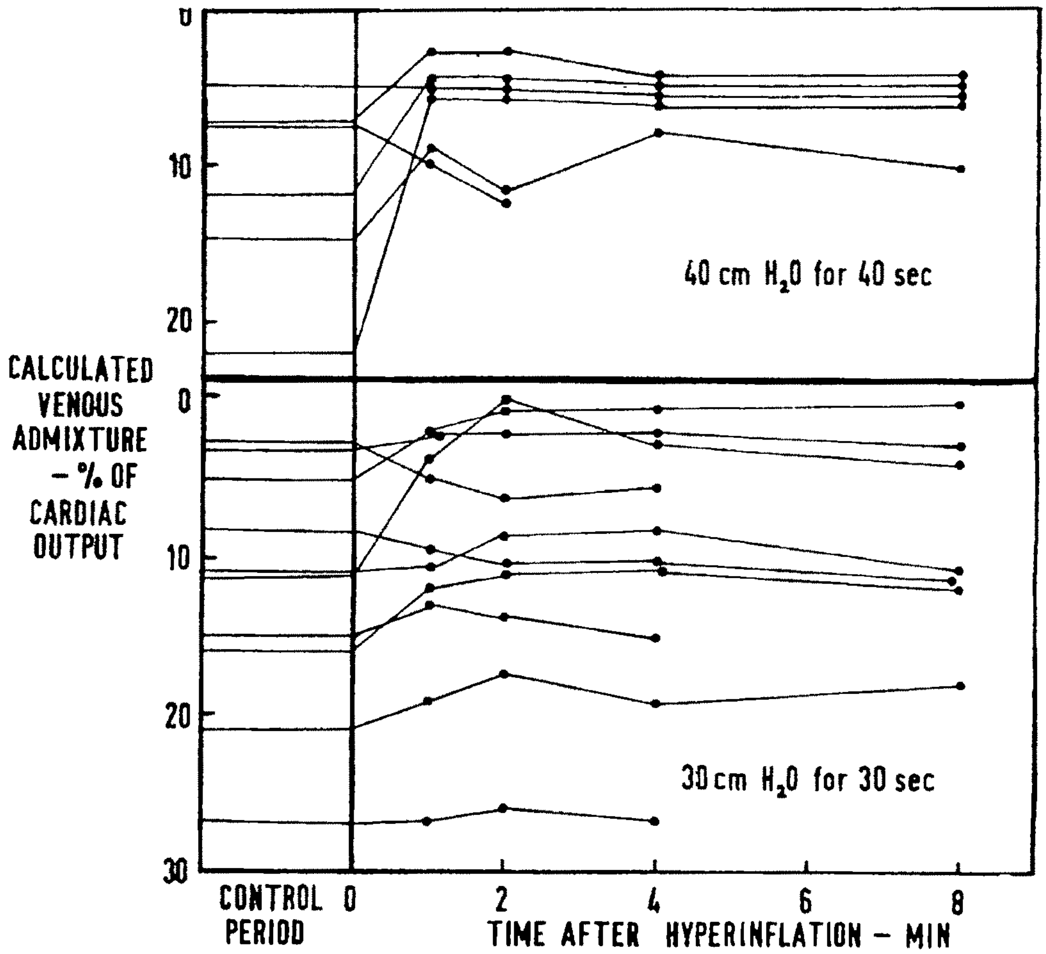

FIG. 6

Sustained hyperinflation caused a reduction of calculated venous admixture in most of the patients when a pressure of 40 cm H_2O was applied for 40 seconds but not when a pressure of 30 cm H_2O was applied for 30 seconds.

conducive to atelectasis and that high alveolar levels of Po_2 may encourage absorption atelectasis in the manner observed by Nunn et al. (1965).

It is not without interest that the alveolar-arterial Po_2 difference caused by venous admixture of a given magnitude is increased by the shift in the dissociation curve, due to reduction in Pco_2 caused by hyperventilation. On the assumption that the arteriovenous oxygen difference remains constant, the magnitude of this effect has been calculated for different values of alveolar Po_2 (table V). The effect is negligible when the end-pulmonary capillary blood approaches full saturation but becomes progressively more important as the Po_2 falls.

In the previous study of patients breathing spontaneously (Nunn, 1964) distinction was made between shunting and inequality of ventilation/perfusion ratios (factors 3 and 4). This was possible because observations were made over a range of Po_2 which permitted some distinction between these two causes of increased alveolar-arterial Po_2 gradient. In the present study, however, the range of alveolar Po_2 is smaller and it is not possible to make the distinction. Shunting is the only possible cause of the gradient in Group II and a similar amount of venous admixture is sufficient to account for the greater part of the gradient in Group I without the need to invoke inequality of ventilation/perfusion ratios as a major factor. We have not excluded the possibility that marked inequality of ventilation/perfusion does exist under the conditions of the study, but it would only be expected to exert an appreciable influence on the alveolar-arterial Po_2 gradient at a level of alveolar Po_2 considerably

TABLE IV

Comparison of venous admixture found in various studies.

	Studies near normal arterial Po$_2$		Studies at high Po$_2$	
	Alveolar Po$_2$ (mm Hg)	Calculated venous admixture (%)	Alveolar Po$_2$ (mm Hg)	Calculated venous admixture (%)
Conscious man				
Campbell, Nunn and Peckett (1958)	102	6.2	—	—
Cole and Bishop (1963)	107	3.6	653	1.2
Nunn and Bergman (1964)	106	5.7	665	1.3
Anaesthetized patients (spontaneous respiration)				
Stark and Smith (1960)	—	—	584	17.8
Nunn (1964)	149	11.3	660	13.5
Anaesthetized patients (artificial ventilation)				
Campbell, Nunn and Peckett (1958)	102	9.3	—	—
Stark and Smith (1960)	—	—	615	22.7
Sykes, Young and Robinson (1965) Group I	133	10.7	—	—
Group II	133	8.6	—	—
Present study	155	9.3	662	10.8

To facilitate comparisons, all calculations in this table are based on an assumed arteriovenous oxygen content difference of 3.5 vols per cent, although in some cases the original authors have not used this value.
Additional studies have been reviewed by Cole and Bishop (1963) and Laver and Seifen (1965).

TABLE V

Effect of Pco$_2$ on the relationship between alveolar-arterial Po$_2$ gradient and shunt (values for patient with 10 per cent shunt).

	Alveolar-arterial Po$_2$ gradient (mm Hg)	
Alveolar Po$_2$ (mm Hg)	With Pco$_2$ 40 mm Hg	With Pco$_2$ 20 mm Hg
200	85	90
150	50	65
100	20	30

lower than that observed in the present study (Farhi and Rahn, 1955). Such levels may arise in the immediate postoperative period.

Table VI compares the studies during spontaneous and artificial respiration in order to demonstrate the effect of hyperventilation on the arterial Po$_2$. There are a number of effects which do not all act in the same direction. In the first place, the alveolar Po$_2$ was higher for a lower inspired oxygen concentration when the patient was hyperventilated. However, venous admixture was greater during spontaneous respiration but, due to the shift in the dissociation curve, the alveolar-arterial Po$_2$ difference was actually slightly smaller. The major influence of hyperventilation was thus on the alveolar Po$_2$, and in these two groups of patients comparable levels of arterial Po$_2$ were obtained with an inspired oxygen concentration which was appreciably lower for the patients who were ventilated artificially. The requirement for inspired oxygen concentration is therefore lower for patients ventilated artificially according to the minute volume attained. Twenty-five per cent oxygen appears adequate for the average patient ventilated at 10 l./min, but the wide variation in individual alveolar-arterial Po$_2$ gradients is such that at least 31 per cent oxygen is required to ensure normal arterial Po$_2$ in the majority of patients anaesthetized under these circumstances. This accords with the formula given for anaesthesia with spontaneous respiration (Nunn, 1964).

TABLE VI
Effect of hyperventilation on arterial Po_2

	Spontaneous respiration (Nunn, 1964) (13 observations)	Artificial ventilation (present study) (45 observations)
Mean inspired O_2 conc. (%)	28.43	25.17
arterial Pco_2 (mm Hg)	49.9	27.4
alveolar Po_2 (mm Hg)	149	155
venous admixture (%)	11.3	9.3
alveolar-arterial Po_2 difference (mm Hg)	42	52
arterial Po_2 (mm Hg)	107	102

$$\text{Required inspired oxygen concentration (\%)} = 28 + \frac{33}{\text{minute volume (l./min BTPS)}}$$

There is certainly no support for the belief that 21 per cent oxygen will ensure normal arterial Po_2 in the majority of patients anaesthetized under the conditions of this study.

The marked difference in degree of scatter between alveolar and arterial Po_2 is shown in figure 7, in which these parameters are plotted against inspired oxygen concentration. It will be seen that alveolar Po_2 (o) approximates very closely to a linear function of the inspired oxygen concentration and could, therefore, be predicted with a high level of accuracy. However, arterial Po_2 (x) shows wide scatter and poor correlation with the inspired oxygen concentration within the range 21–31 per cent. It is thus clear that venous admixture constitutes the major factor influencing arterial Po_2 during artificial ventilation at a minute volume of about 10 l./min within the range of inspired oxygen concentration 21–31 per cent (fig. 8). Even during spontaneous respiration with variable ventilation (Nunn, 1964) there is still a high degree of correlation between arterial Po_2 and venous admixture.

Our results for alveolar-arterial Po_2 gradient are intermediate between those in the early studies of Campbell, Nunn and Peckett (1958) and Stark and Smith (1960). More recently, other studies of the effect of anaesthesia upon arterial Po_2 have been published. Conway and Payne (1964) have reported mean values within

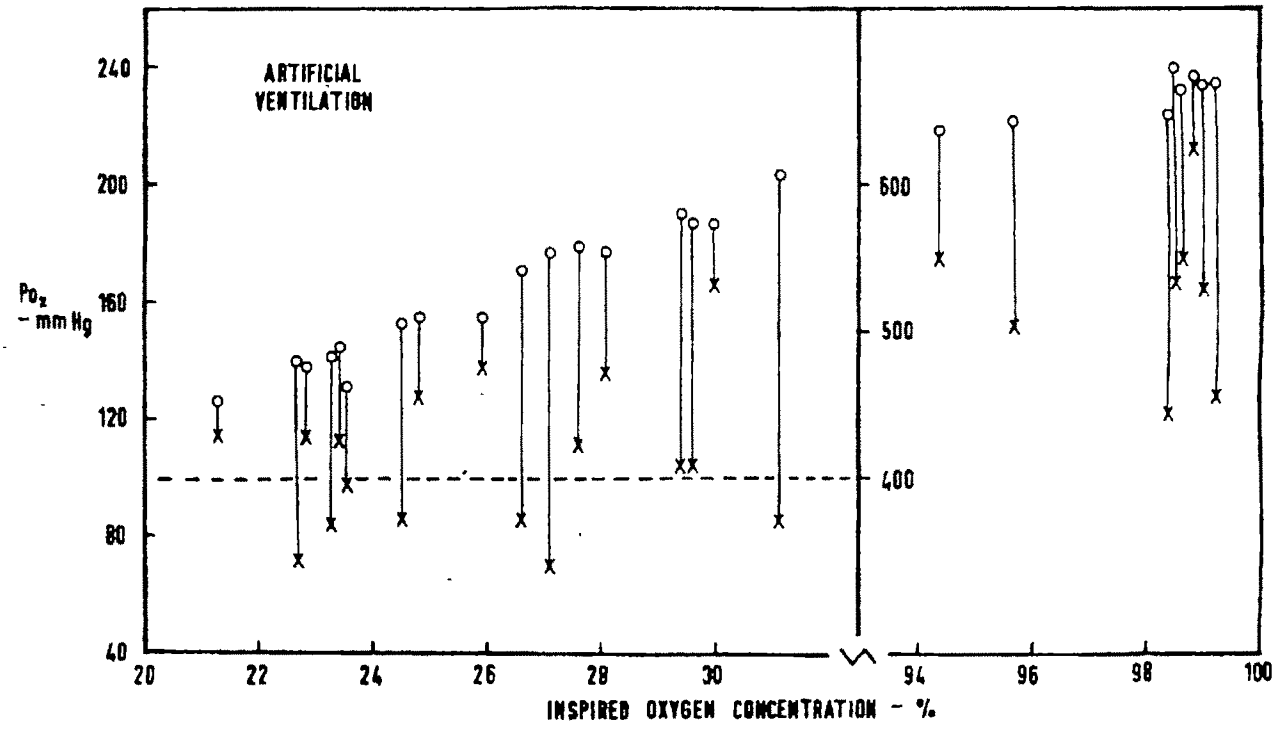

FIG. 7
Alveolar (o) and arterial (x) Po_2 plotted against inspired oxygen concentrations. The vertical lines join observations made on the same patients. While the alveolar Po_2 approximates closely to a linear function of the inspired oxygen concentration, the arterial Po_2 shows wide individual variations.

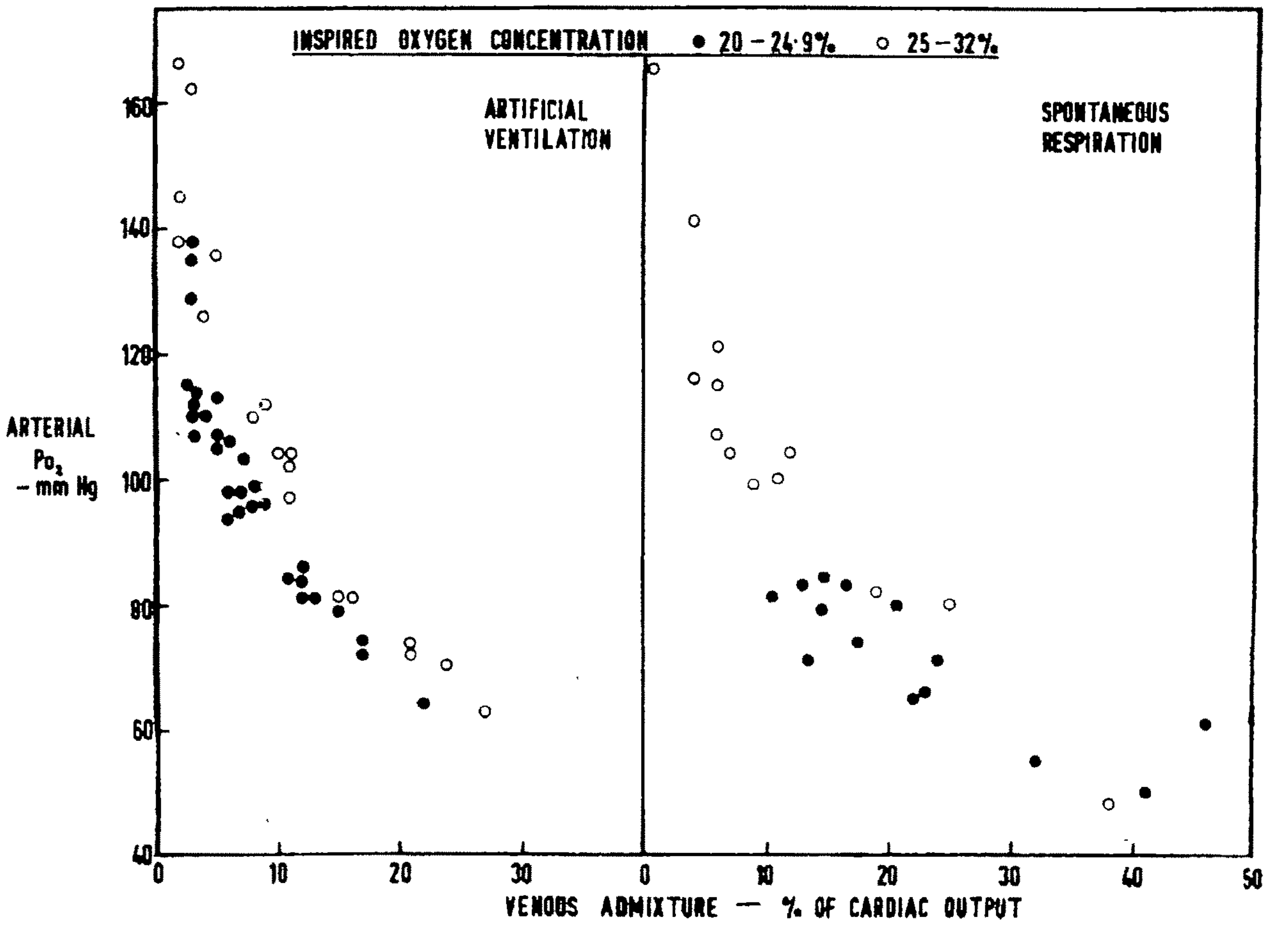

FIG. 8
Arterial Po_2 plotted against calculated venous admixture for patients ventilated artificially (present study) and breathing spontaneously (Nunn, 1964).

the range 80–100 mm Hg during anaesthesia with artificial ventilation using a Waters to-and-fro semiclosed gas circuit. The oxygen concentration of the fresh gas supply was 25 per cent but the gas circuit is known to cause rebreathing and it is therefore difficult to estimate the concentration of oxygen in the inspired gas. Nevertheless, their values are clearly compatible with our own. Two studies by Theye and Tuohy (1964a, b) have investigated artificial ventilation employing 35 per cent oxygen in the inspired gas mixture. During halothane anaesthesia the mean alveolar Po_2 was 204 mm Hg, and the arterial Po_2 126 mm Hg, results which accord very well with an extrapolation of the lefthand segment of figure 7 in the present paper and imply a similar degree of venous admixture. During methoxyflurane anaesthesia the alveolar Po_2 appeared higher and the mean arterial Po_2 lower, indicating a considerably larger alveolar-arterial Po_2 gradient in the latter study although it is not clear whether this could be explained by the nature of the anaesthetic agent. We are in agreement with these authors that arterial Pco_2 and alveolar Po_2 remain within close limits during anaesthesia and artificial ventilation with a particular concentration of oxygen in the inspired gas. The arterial Po_2, however, varies between such wide limits that its value cannot be predicted. Theye and Tuohy report extreme variations of arterial Po_2 amounting to about 100 mm Hg in spite of maintaining a constant concentration of oxygen in the inspired gas. Taylor, Scott and Donald (1964) have studied six young healthy patients during anaesthesia for short minor operations. In spite of a fresh gas supply containing more than 95 per cent oxygen, the mean arterial Po_2 was only 380.5 mm Hg after 10 minutes, falling to 332.8 after 20 minutes. Unfortunately they do not give details which would permit exclusion of the possibility of rebreathing as a factor causing the low arterial Po_2. If there was no rebreathing, their results would suggest a shunt of the order of 20–25 per cent of total pulmonary blood flow. Sykes, Young and Robinson (1965) have reported a study which is very similar to our own, both as regards conditions and the quantities which were studied. Their values for alveolar and arterial Po_2 may be interpolated in figure 7 and will be found to be entirely consistent with our own data. Their values for venous admixture are lower than ours due to their assumption of a greater arteriovenous oxygen content difference. They produce some evidence that hyperventilation reduces the venous admixture.

In 1963, Bendixen, Hedley-Whyte and Laver reported progressive falls of arterial Po_2 during anaesthesia. This change appeared to be explicable by the same mechanism that caused progressive fall of compliance of the lungs of anaesthetized dogs (Mead and Collier, 1959). Our results have not confirmed this finding in patients under the age of 43 while in older patients the changes were significant but seldom dramatic (fig. 3). It is perhaps important to stress that Bendixen Hedley-Whyte and Laver (1963) found the rate of fall of arterial Po_2 to be directly related to the arterial Pco_2 and the levels of arterial Pco_2 in their study are considerably higher than those encountered in current British clinical anaesthetic practice when artificial ventilation is used. Only slight changes occurred in patients whose Pco_2 lay within the range encountered in this study while the larger falls were restricted to patients whose Pco_2 was at higher levels than those we have studied. We now find that there are a number of other studies which support our belief that the progressive fall of Po_2 during anaesthesia is perhaps less marked than has been suggested. Theye and Tuohy (1964a) have studied changes in Po_2 during anaesthesia and did not observe any pattern of change in alveolar-arterial Po_2 gradients with time in individual patients. Askrog et al. (1964) have reported serial changes during anaesthesia and, although they do not define the limits within which they controlled the concentration of oxygen in the inspired gas, their results, prolonged over 150 minutes, did not show progressive falls of arterial Po_2 of the type reported by Bendixen and his colleagues. Additional evidence has now been obtained by Sykes, Young and Robinson (1965). Patients in their Group I were maintained at reasonably constant levels of ventilation, arterial Pco_2 and alveolar Po_2, but showed no change in alveolar-arterial Po_2 gradient with time (42 mm Hg at 25 minutes and 41.6 mm Hg at 80 minutes). We do not deny that progressive atelectasis may occur in some patients during anaesthesia but we do not believe that this is an inevitable feature of anaesthesia in all patients.

Our attempts to raise the arterial Po_2 by measures designed to re-expand atelectatic areas of lung have been disappointing. Raising of the expiratory pressure (fig. 5) was suggested by the important pioneer study of Frumin and associates (1959). This study was carried out before the introduction of the polarograph and it is clear that there was difficulty in deducing the arterial Po_2 from the saturation when the oxygen values were located on the flat part of the dissociation curve. Nevertheless they showed a rise of arterial Po_2 of 7 mm Hg when the patient was caused to exhale through a 3-mm orifice and a rise of 10 mm Hg when the expiratory pressure was changed from -5 to $+5$ mm Hg. Bendixen, Hedley-Whyte and Laver (1963) and Bendixen, Bullwinkel, Hedley-Whyte and Laver (1964) have demonstrated impressive improvements in arterial Po_2 following manual hyperinflation. In their earlier paper, they show that inflations to 40 cm H_2O were more satisfactory than to 20 or 30 cm H_2O and we appear to have found a marked difference between 30 and 40 cm H_2O (fig. 6). We have favoured a sustained inflation because this appeared to be more effective at thoracotomy when the re-expansion could be watched directly. However, it may well be that intermittent inflation is more effective and it is likely that further work will be needed to establish the most satisfactory form of inflation.

There now appears to be very strong evidence of an increase in both physiological deadspace and venous admixture during anaesthesia. There has, however, been little progress in determining the cause of these abnormalities. Since these disorders are commonly found to be associated in chronic respiratory disease it has been tempting

TABLE VII

Inert gas exchange.

Time after induction (min)	Predicted N_2O uptake (ml/min STPD)	Predicted N_2 elimination (ml/min STPD)	Predicted inert gas exchange (ml/min STPD)	Observed inert gas exchange (ml/min STPD)
20	224	8	216	250
40	158	5	153	150
60	129	4	125	120

to suggest that anaesthesia produces a reversible emphysema-like state of the lungs and measurements of deadspace and venous admixture certainly produce a picture which is quite typical of emphysema. However, this outlook is untenable for the following reasons. Firstly, the changes in physiological deadspace and venous admixture during anaesthesia are dissociated from one another. The data of the present study combined with those of Nunn (1964) have been examined to determine the correlation between physiological deadspace and venous admixture in individual patients. There is none. Secondly, the distribution of inspired gas has now been found to be normal during anaesthesia (Bergman, 1963) and defects of distribution are a consistent finding in patients with severe emphysema. Finally, the slope of the expired carbon dioxide concentration (plotted against expired volume) is practically normal during anaesthesia (Nunn and Hill, 1960). This is in contrast to patients with emphysema in whom the capnogram is steeply sloping and characteristic of their condition.

Severinghaus (1954) studied the rate of uptake of nitrous oxide at a constant inhaled concentration of 80 per cent. and concluded that nitrous oxide uptake per minute is given by the expression: $\dot{V}_{N_2O} = 1000\ t^{-0.5}$ (t=time in minutes). He also concluded that nitrogen elimination should be 1/30 that of N_2O uptake because of relative solubilities of the two gases. Since in the patients of Group I in the present study, inhaled nitrous oxide concentration was close to 80 per cent, it is of interest to compare observed inert gas exchange with that predicted from Severinghaus's data (table VII).

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LES FACTEURS INFLUENCANT LA TENSION DE L'OXYGENE ARTERIEL PENDANT L'ANESTHESIE AVEC VENTILATION ARTIFICIELLE

SOMMAIRE

Les facteurs influençant l'oxygénation du sang arteriel ont été étudiés chez 26 malades pendant une anesthésie de routine avec ventilation artificielle. Le volume-minute moyen était de 10 l./min et la Pco$_2$ artérielle de 27 mm Hg. La consommation moyenne d'oxygène était de 215 ml/min (STPD), et l'espace mort physiologique 36 pour cent du volume courant (aucun pourcentage ne pouvaont être fait pour le volume de l'air shunté par la sonde intratrachéale). Pour de fortes concentrations d'oxygène inspiré, le gradient moyen de la Po$_2$ alvéolaire-artériel était de 145 mm Hg ce qui correspond à un shunt calculé de 11 pour cent. Pour une Po$_2$ alvéolaire de 155 mm Hg, le gradient était de 52 mm Hg, ce qui correspond à un mélange veineux calculé de 9 pour cent. Il n'y a pas eu une augmentation progressive du mélange veineux pendant l'anesthésie chez les malades de moins de 43 ans, mais la plupart des malades plus âgés ont présenté des diminutions et leur changement moyen était significatif. On a tenté de réduire le mélange veineux par l'hyperinflation des poumons. On y est arrivé chez quelques malades, quand une pression de 40 cm H$_2$O était maintenue 40 secondes. Des pressions plus basses et l'emploi d'une pression expiratoire maintenue de 5 cm H$_2$O n'ont pas eu d'effet. Les signes de perturbation de la fonction respiratoire trouvés dans cette étude n'étaient pas notablement différents de ceux obtenus dans une étude comparative chez des malades anesthésiés respirant spontanément.

FAKTOREN, DIE DIE ARTERIELLE SAUERSTOFFSPANNUNG WÄHREND DER NARKOSE MIT KÜNSTLICHER BEATMUNG BEEINFLUSSEN

ZUSAMMENFASSUNG

An 26 Patienten wurden während Routinenarkosen mit künstlicher Beatmung die Faktoren mit Einfluß auf die Sauerstoffsättigung des arteriellen Blutes untersucht. Das mittlere Minutenvolumen betrug 10 l./min und der arterielle Pco$_2$-Wert 27 mm Hg. Der mittlere Sauerstoffverbrauch war 215 ml/min (bei Standardtemperatur- und druck, trocken) und der physiologische Todraum betrug 36 Prozent des Zugvolumens (das Volumen der durch den Endotrachealtubus umgangenen Luftwege wurde nicht berücksichtigt). Bei hohen inspiratorischen Sauerstoffkonzentrationswerten lag das mittlere alveoläre-arterielle Po$_2$-Gefälle bei 145 mm Hg mit einem dazugehörigen errechneten Shunt von 11 Prozent. Bei einem alveolären Po$_2$ von 155 mm Hg betrug das Gefälle 52 mm Hg entsprechend einer errechneten venösen Zumischung von 9 Prozent. Bei Patienten im Alter von weniger als 43 Jahren fand sich während der Anästhesie keine zunehmende Steigerung der venösen Zumischung., aber die älteren Patienten zeigten meist einen Abfall und der Mittelwert der Veränderung war signifikant. Es wurden Versuche unternommen, die venöse Zumischung durch Überdehnung der Lungen zu vermindern. Bei einigen Patienten war dies erfolgreich, wenn ein Druck von 40 cm H$_2$O für 40 Sekunden aufrecht erhalten wurde. Niedrigere Drücke und die Anwendung eines unterstützten Ausatmungsdruckes von 5 cm H$_2$O waren ohne Wirkung. Hinweise für eine entgleiste Atemfunktion, wie sie bei dieser Untersuchung festgestellt wurden, waren kaum merklich verschieden im Vergleich zu den Werten bei einer Vergleichsuntersuchung bei narkotisierten Patienten mit Spontanatmung.

British Journal of Anaesthesia 1998; **80**: 877–879

CORRESPONDENCE

Death in the dental chair - an avoidable catastrophe?

Editor,—I agree with Worthington, Flynn and Strunin that death in the dental chair is catastrophic, and I sincerely hope that it is avoidable.[1] In their editorial the authors make the case for these views most elegantly, but I am a little concerned by their final, and isolated, conclusion that substitution of halothane by sevoflurane is the definitive requirement. All inhalation anaesthetics lower the threshold for arrhythmias. I would accept that the problem is somewhat greater with halothane than with sevoflurane, but I feel they are a little hard on a drug that has served us well for many years. Changing to sevoflurane will have significant cost implications — something that I would be happy to endorse if halothane really is the key cause of death in the dental chair. Arrhythmias with halothane are, in my view, nearly always associated with poorly conducted anaesthesia resulting in either carbon dioxide retention or hypoxaemia. In the dental chair, other factors (notably fear and intense surgical stimulation) are also relevant, but we must recognize that the proper conduct of the anaesthetic remains paramount. Many of the deaths referred to by Worthington, Flynn and Strunin have involved factors of much greater significance than the simple choice of inhalation agent. Sevoflurane will certainly reduce the incidence of arrhythmias, but will it reduce the incidence of avoidable catastrophe?

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1. Worthington LM, Flynn PJ, Strunin L. Death in the dental chair — an avoidable catastrophe? *British Journal of Anaesthesia* 1998; **80**: 131–132.

Editor,—We thank Professor Wildsmith for his interest in our article, and agree with his point that all inhalation anaesthetics lower the threshold for arrhythmias. He is correct to state that the problem is greater with halothane than with sevoflurane; the study carried out by Paris and colleagues[1] found that the incidence of arrhythmias during anaesthesia for dental surgery is much greater with halothane (62%) than with sevoflurane (26%). We would, however, dispute the point that halothane arrhythmias are nearly always associated with poorly conducted anaesthesia. Again referring to the study by Paris and colleagues, only one of the 50 patients who received halothane suffered a reduction in oxygen saturation to below 90%, only five patients coughed and only four had any degree of breath-holding. It is therefore unlikely that a 62% incidence of arrhythmias can be attributed solely to poorly conducted anaesthesia resulting in carbon dioxide retention or hypoxaemia. In a study by Casson and Jones,[2] which found that the incidence of arrhythmias during dental surgery was greater with halothane than with isoflurane or enflurane, it was noted that there were no significant differences in the end-tidal carbon dioxide concentration between the three groups and that the levels did not exceed 6.6 kPa in any patient. This is further evidence against the argument that the arrhythmias seen with halothane are caused by hypercarbia. Unfortunately, we cannot say if changing to sevoflurane will reduce the number of deaths in dental anaesthesia, but as Professor Wildsmith points out, using sevoflurane will certainly reduce the number of arrhythmias. In particular, ventricular arrhythmias — which are more likely to progress to ventricular fibrillation — will be reduced.[3] Coplans and Curson found that 40% of deaths that occurred in dental practice were associated with a sudden cardiovascular collapse and 60% were principally attributable to respiratory problems.[4] If use of a less arrhythmogenic drug can reduce the number of cardiac-related deaths, then surely a relatively small increase in cost per procedure is worthwhile.

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1. Paris ST, Cafferkey M, Tarling M, Hancock P, Yate PM, Flynn PJ. A comparison of sevoflurane and halothane for outpatient dental anaesthesia in children. *British Journal of Anaesthesia* 1997; **79**: 280–284.
2. Casson WR, Jones RM. Cardiac rate and rhythm during anaesthesia for dental extraction. A comparison of halothane, enflurane and isoflurane. *British Journal of Anaesthesia* 1985; **57**: 476–481.
3. Cranefield PF. Ventricular fibrillation. *New England Journal of Medicine* 1973; **289**: 732–736.
4. Coplans MP, Curson I. Deaths associated with dentistry. *British Dental Journal* 1982; **153**: 357–363.

Editor,—We read the editorial on death in the dental chair[1] with great interest, and note and agree with all the points made by the authors. An argument against the introduction of sevoflurane into high street anaesthesia for dentistry is cost. However, there is more to the issue than the difference in cost per unit volume and different MACs. The varying induction characteristics of the two anaesthetic agents make such comparison unrealistic. We work as a team in the practice of dental-chair general anaesthesia in hospital and in general dental practice. In the former venue, sevoflurane is used exclusively; in the latter, halothane. We are ideally placed to compare the cost of these agents. Our small study was very simple. We measured the mass of volatile agent used for a list of simple exodontias, calculated the volume of agent used and thereby the cost, and divided this by the number of children anaesthetized. The fresh gas flow rate was held constant. We found that, in our hands, the cost of the agent for this form of anaesthesia is 30p per patient using halothane, and £2.86 per patient using sevoflurane. We would add that nitrous oxide is not used, just the volatile agent in oxygen. Although the cost of sevoflurane is higher, as expected, it is also true that it is not prohibitively so, and is covered even by the low remunerative rates provided by the Dental Practice Board. In private practice, there is probably no need to adjust one's scales either. Before reading this editorial and carrying out our investigation, we had been attempting to persuade our local Director of Dental Public Health to subsidize the introduction of sevoflurane into high-street practice. If this subsidy is not rapidly forthcoming, we shall ourselves make arrangements to introduce sevoflurane for our patients.

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1. Worthington LM, Flynn PJ, Strunin L. Death in the dental chair: an avoidable catastrophe? *British Journal of Anaesthesia* 1998; **80**: 131–132.

Optimum technique for delivery of extradural analgesia during labour

Editor,—I was interested in the study by Duncan and colleagues, who found that extradural analgesia was better when given by regular automated bolus injection rather than by continuous infusion.[1] This finding has implications for extradural analgesia during labour, for which there has been a perception[2] that continuous infusion is probably the preferred method. However, rather than moving towards automated bolus injections in this setting, the best choice may be to return to top-ups given by midwives, but on a regular basis rather than on demand. This should confer all the benefits found by Duncan and colleagues, but with the following additional advantages: it is arguably at least as safe as automated bolus dosing; it is simple, of low technology and cheap; and it is an adaption of a tried and tested method that is in place in many units.

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1. Duncan LA, Fried NJ, Lee A, Wildsmith JAW. Comparison of continuous and intermittent administration of extradural bupivicaine for analgesia after lower abdominal surgery. *British Journal of Anaesthesia* 1998; **80**: 7–10.
2. Hicks JA, Jenkins JG, Newton MC, Findley IL. Continuous epidural infusion of 0.075% bupivicaine for pain relief in labour. A comparison with top-ups of 0.5% bupivicaine. *Anaesthesia* 1988; **43**; 289–292.

Editor,—We thank Dr Mills for his interest and comments on our article. As mentioned in our paper, attempts have been made to provide postoperative extradural analgesia using regular, nurse-administered bolus injections of local anaesthetic.[1] However, because of the many other demands on nursing time, injections were not given often enough to maintain analgesia and this method ultimately failed. We therefore designed our study to take advantage of recent technological advances in infusion pump design, and thus avoid putting further pressure on nursing staff. The provision of extradural analgesia in labour differs in many ways from its use for the relief of postoperative pain, but we believe many of the problems with nurse-administered injections exist in the obstetric setting. Further, we believe many nurses are reluctant to give analgesic drugs when patients are not in pain.[2] Therefore, in our view, the use of appropriate infusion pumps to deliver regular bolus doses of local anaesthetic extradurally may be worthy of study in the obstetric population.

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1. Scott DB, Schweitzer S, Thorn J. Epidural block in postoperative pain relief. *Regional Anesthesia* 1982; 7:135–139.
2. The Royal College of Surgeons of England and The College of Anaesthetists. *Commission on the provision of surgical services. Report of the working party on pain after surgery*. Royal College of Surgeons. London: September 1990.

Inhalation anaesthetics and the Medtronic Maxima *Plus* membrane oxygenator

Editor,—Most membrane oxygenators used in clinical practice contain microporous membranes, which are made from either polyethylene or polypropylene. Different types of oxygenator vary because of differences in the manufacturing process or in the size of the pores in the membrane. The Medtronic Maxima *Plus* PRF hollow-fibre oxygenator is used routinely for blood gas exchange during cardiopulmonary bypass. Total oxygen transfer is enhanced with this oxygenator, compared with the original Maxima model, because the outside diameter of the hollow, microporous polypropylene fibres within the oxygenator is reduced, thus providing a larger membrane surface area for transfer of oxygen.[1] We conducted a study to determine if contact with inhalation anaesthetic agents has deleterious effects on these fibres, and can report that it appears not to do so. The polycarbonate outer shell of the oxygenator was removed to reveal the polypropylene fibres. Some of these fibres were placed in liquid sevoflurane, some for 3 h and others for 1 week. Fibres were also exposed to enflurane, isoflurane and the solvent, acetone, for the same periods. After exposure, the fibres were examined under a high-resolution light microscope. Light-microscopic examination revealed no change in the structure or integrity of the fibres after short-term or long-term exposure to the three anaesthetic agents and acetone. We know of no evidence that inhalation anaesthetics damage oxygenator fibres, and in our short study, we found that exposing polypropylene, an inert substance, to saturating concentrations (concentrations in excess of those achieved in clinical practice) of three anaesthetic agents caused no visible structural damage. We have not carried out functional studies on fibres subjected to anaesthetic exposure. However, it appears that inhalation anaesthetics do not cause structural damage to the oxygenator fibres and we conclude, therefore, that oxygen transfer is unlikely to be impaired when they are used during cardiopulmonary bypass.

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1. Fried DW, DeBenedetto BN, Zombolas TL, Leo JJ. Clinical evaluation of the Medtronic Maxima *Plus* membrane oxygenator. *Perfusion* 1994; **9**: 363–372.

A leak of concern

Editor,—Concerning the matter of potentially important, but not uncommon, leaks from anaesthetic machines, I should like to bring to your attention the possibility of leaks from soda-lime canisters of the type made by Demeca, which are widely used on the Blease 8200s circle scavenged anaesthetic machine.

A leak occurred after reassembly of such a canister following routine cleaning. The canister, of 1-kg size, is serviced by Blease under contract but is cleaned in the workplace by theatre staff. The leak was discovered at the start of a neurosurgical list; the anaesthetist checked the machine and declared the presence of an obvious leak without determining the source. An operating department assistant was informed but no repair was made. A second anaesthetist then used the machine without incident to anaesthetize an adult of 75 kg for a 2-h procedure.

The next procedure was upon a 15-kg child aged 2 yr. It was immediately apparent, because of significant difficulty in maintaining an adequate tidal volume, that a major leak was present. On careful search, it was found to arise from the soda-lime canister. The canister was replaced and the procedure continued without further incident.

Examination revealed the canister to be leaking from the rubber "O"-ring at the junction of the plastic top section with the metal lower section. On initial inspection, the canister appeared sound (fig. 1) but pressure with forceps on "O"-ring revealed a gap where the ring had been incorrectly seated (fig. 2).

With the "O"-ring properly fitted, there was no leak. The manufacturers confirmed that this complication had not been reported before. I therefore offer a warning that the reassembly of soda-lime canisters requires close attention to avoid the problem that I have described, which could be compensated for in an adult but represented a great risk in a small child. These canisters must be reassembled carefully after cleaning and this complication borne in mind as the possible source of a major leak.

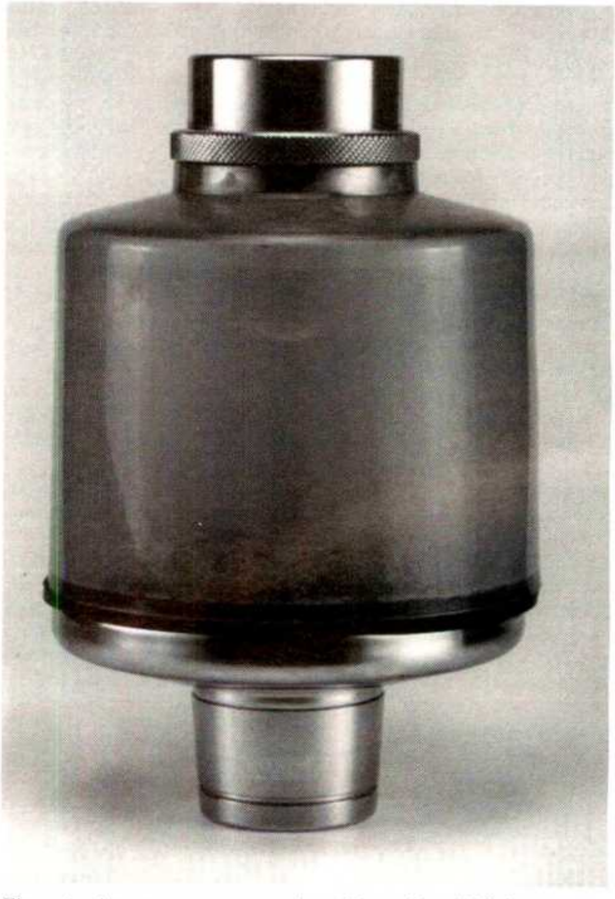

Figure 1 Apparent correct seating of the rubber "O" ring.

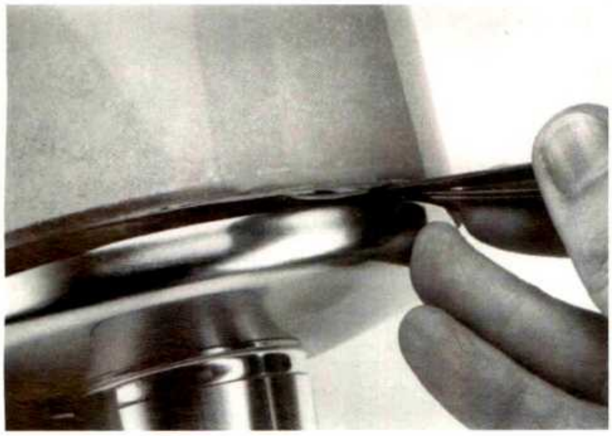

Figure 2 Demonstration of incorrect seating of rubber "O" ring.

Equipment that is disassembled should have screw-on male and female parts in seals, rather than slip-together parts. If canisters were made so that the parts fitted together like those of a "Chinese puzzle", such that an incorrectly assembled canister could not be used on an anaesthetic machine, this would prevent leaks of this sort. If rubber seals are unavoidable, these should be checked regularly for wear and porous changes. The need to check the anaesthetic machine at the start of every case needs great emphasis in a busy operating suite, where several different anaesthetists are using the same machine. A preoperative test to detect this possibility needs to be developed, and then recommended widely to help avoid the problem. Fresh gas flow observation to provide a given pressure limit while checking the breathing system before use is one possible method but, unfortunately, there are no fail-safe methods for detecting leaks. The presence of a leak should be unacceptable to any anaesthetist and preclude the use of any anaesthetic machine until the cause is detected and corrected.

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BOOK REVIEWS

Management of the Elderly Surgical Patient. Problems in Anaesthesia Vol. 9, No. 4. P. J. Dauchot and H. Cascorbi (editors). Published by Lippincott-Raven, Philadelphia. Pp. 588. Indexed; illustrated. Price $34.00.

This American text is part of a series of publications on "Problems in Anaesthesia" (vol. 9, no. 4). The guest editors of *Management of the Elderly Surgical Patient* are Paul J. Dauchot and Helmut Cascorbi from the Case Western Reserve University School of Medicine, Cleveland, Ohio, and the issue contains contributions from several other experts in the field. The editors' declared purpose is to cover important aspects of the perioperative condition of the elderly patient, and provide more fundamental knowledge about the aging process. This the book largely succeeds in doing.

The first chapters cover the theories and mechanisms of aging and the effects of ageing on body composition and metabolism, the cardiovascular and autonomic nervous system, and the respiratory system and central nervous system; they all provide good background information for the practising anaesthetist. The chapters on "Pharmacology and pharmacokinetics of aging" and "Intraoperative anaesthetic agents" provide a clear exposition of the differing effects drugs used in anaesthesia have in this population. The chapter on preoperative preparation gives examples of detailed guidelines proposed in the USA, such as an algorithm for preoperative cardiac evaluation for noncardiac surgery. However, there is little consideration of the patient's cognitive and psychological condition or self-assessment of his or her condition, or of the greater need to ensure that elderly patients understand the risks and benefits of surgery and anaesthesia in their particular case.

The chapter on "General versus regional anaesthesia" is an excellent exposition of the present position and clearly identifies that most perioperative complications in older patients occur postoperatively; the need for further outcome studies to be undertaken is noted. The chapter draws attention to studies that indicate that "failure to rescue patients from adverse perioperative events is emerging as a better measure of the contribution of an anaesthesia provider to the quality of care than the actual complication rate" and that "the more board-certified anaesthesiologists are involved in the perioperative process at a hospital, the greater the rescue rate and the lower the death rate."

Safety issues in conscious sedation are well addressed, with examples of well defined multidisciplinary approaches to hospital-wide protocols. The authors draw on the greater experience in the USA of outpatient procedures in the elderly and the risk factors to be considered. The suggestion that mental dysfunction may be reduced in severity when elderly patients undergo surgery on an outpatient basis is of importance. The final chapter on pain management emphasizes the need to identify the cause before instituting management.

Overall, this is an informative and well presented text that can be recommended to trainees and experienced anaesthetists. It does not aim to be a fully comprehensive review of the role of the anaesthetist in the care of the elderly surgical patient and does not cover all aspects of their care. Trainees will need to read other texts, on topics such as high-dependency care and intensive care, recommended practice in particular surgical conditions, and ethical matters.

A. E. Edwards

Principles and Practice of ICU Monitoring. M. J. Tobin (editor). Published by McGraw-Hill, Maidenhead. Pp. 1525; indexed; illustrated. Price £105.00.

There are many texts of varying shapes and sizes that discuss monitoring, but this is an extraordinary book in a different league. Physically, it is impressively large and heavy. It successfully covers most aspects of intensive care monitoring, as one might expect in a volume of this size, but it also contains much unexpected but valuable information. The introductory sections on the history of monitoring and the underlying principles of measurement are extremely well written. They are easy to read and informative. In particular, two chapters — the goals and indications of monitoring and the principles of measurement — should be compulsory reading for all trainees in intensive care. The book is well planned and well laid out. Coverage of each area is comprehensive, including not only mainstream monitoring systems and techniques but also those being evaluated. The background and technology of each type of monitoring, its goals, aspirations and shortfalls, are discussed. Current controversies are highlighted and the arguments presented. While some chapters are written by acknowledged enthusiasts in their field, most of them review their subjects in a surprisingly rigorous and critical fashion, suppressing any anticipated bias. Consistently throughout the book, the information contained is current in this rapidly progressive field, which is an achievement in itself. Referencing is comprehensive but sensible throughout. Each chapter is of high quality and there are, in my opinion, no disappointing areas. This is remarkable for so large a book.

I have no criticisms of the book other than its weight, which is impressive. It is undoubtedly the monitoring reference book for the 1990s and no intensive care facility should be without a copy. Its content will undoubtedly age rapidly, as the editor admits, but for the next few years it will be a solid reference text in every sense of the word. I am privileged to have had the opportunity to review what I consider will become a classic text.

N. Soni

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